Volume 7 **Neurology** *Number 4*

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1. Livingston, S., and Petersen, D.: New England J. Med. *254*:327 (Feb. 16) 1956.
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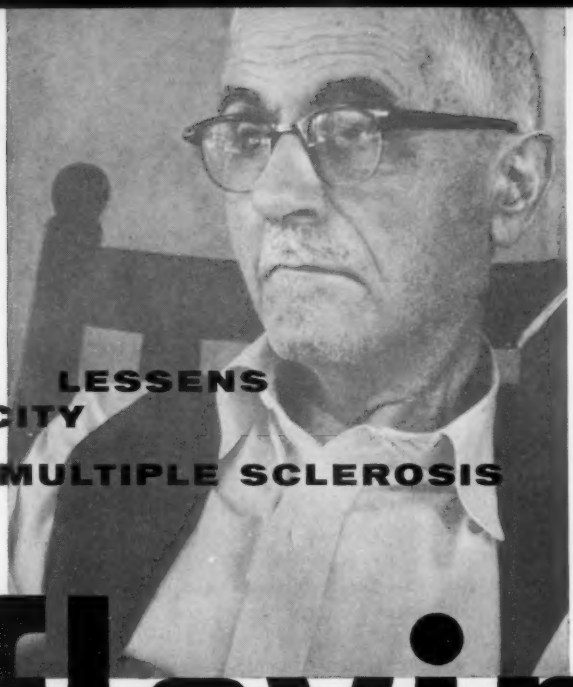

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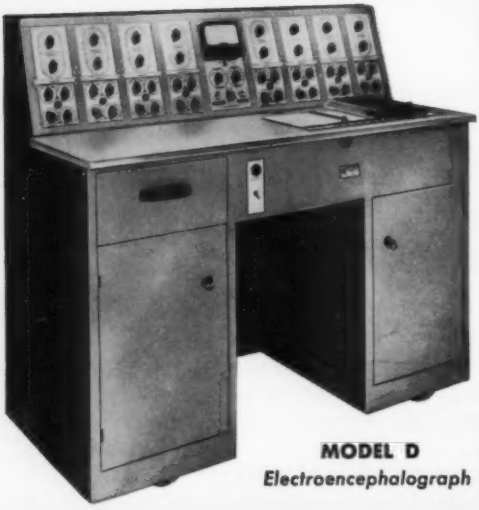

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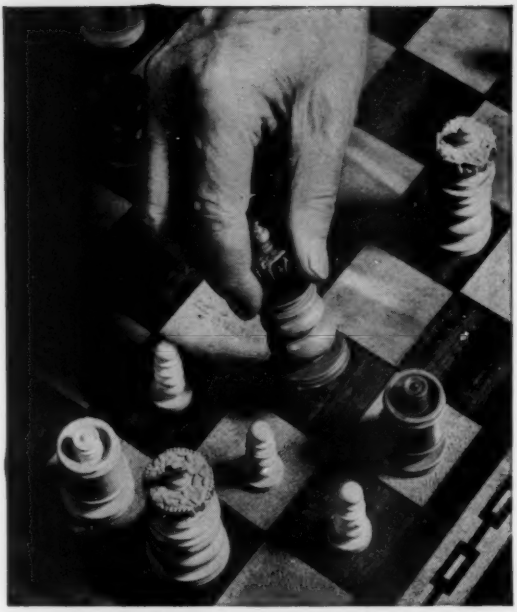

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Volume 7 Neurology *Number 4*

Occlusion of the Carotid Circulation

Pathologic Considerations

Richard G. Berry, M.D. and Bernard J. Alpers, M.D.

THE PROBLEM of internal carotid artery occlusion has aroused great interest in recent years, with attention centered largely on clinical recognition of the condition. Study of the brains of those who have died of this disorder indicates that, in addition to problems of diagnosis, there are also important issues relating to pathogenesis and to cerebral circulation. Internal carotid artery occlusion affords a striking opportunity to study problems of cerebral blood supply, and for this reason we report a group of 21 autopsy specimens in an attempt to clarify some of the problems relating to the blood supply of that portion of the brain which is fed by the internal carotid artery. The examples of internal carotid artery occlusion in this series provide good material for speculation because of their varied causes and the variability in their survival periods.

ANALYSIS OF MATERIAL

The brain specimens in the 21 cases of internal carotid occlusion comprising this series were received in the neuropathology laboratory from the general pathology service of a large general hospital. Because the neurologic and neurosurgical services of this institution are interested in a study of intracranial aneurysms, many specimens of such vascular anomalies were included and a relatively high percentage of internal carotid artery ligations were present. The gross and microscopic features of the pathology of the 21 brains have been examined in each case. In many of the specimens, as part of a separate study, the anatomic features of the circle of Willis were evaluated. Detailed clinical data are omitted except in those cases where such data may help in understanding the pathogenesis of the lesions.

From the department of neurology, Jefferson Medical College, Philadelphia, Pennsylvania.
Read at the eighth annual meeting of the American Academy of Neurology, St. Louis, April 28, 1956.

TABLE 1

INTERNAL CAROTID OCCLUSION

"SPONTANEOUS" THROMBOSIS

Case	Age	Sex	Side	Survival after Occlusion	Circle of Willis: Anatomic Variations	Circle of Willis: Arterio-sclerosis	Site of Occlusion: Neck	Site of Occlusion: Siphon	Site of Occlusion: Middle Cerebral	Site of Occlusion: Anterior Cerebral	Pathologic Lesions: Middle Cerebral	Pathologic Lesions: Anterior Cerebral	Pathologic Lesions: Posterior Cerebral
1	57	F	right	21 hours	(a)	+++	+	+	+	—	+	—	—
8	65	M	left	2½ days	(b)	++++	?	+	+	+	+	+	—
16	60	F	left	13 days	(c)	++	C.C.	—	—	—	+	—	—
19	73	M	right	2½ months	(d)	+++	?	+	+	—	+	—	—
21	55	M	left	46 months	?	++++	?	+	+	—	+	—	—

(a) Right posterior communicating smaller than left.
(b) Both posterior communicatings and anterior communicating stringlike.
(c) Posterior cerebral derived from internal carotid, bilaterally.
(d) Right posterior communicating stringlike.
C.C.=Common carotid.

TABLE 2

INTERNAL CAROTID OCCLUSION

EMBOLIC OCCLUSION

Case	Age	Sex	Side	Survival after Occlusion	Circle of Willis: Anatomic Variations	Circle of Willis: Arterio-sclerosis	Site of Occlusion: Neck	Site of Occlusion: Siphon	Site of Occlusion: Middle Cerebral	Site of Occlusion: Anterior Cerebral	Pathologic Lesions: Middle Cerebral	Pathologic Lesions: Anterior Cerebral	Pathologic Lesions: Posterior Cerebral	Source of Embolism
5	60	F	right	2 days	?	+	?	+	+	—	+	—	—	Rheumatic heart disease; uricular fibrillation.
7	65	M	left	2¼ days	?	++	?	+	+	+	+	+a	—	Rheumatic heart disease; auricular fibrillation; old left auricle thrombus.
12	73	F	left	5 days	N.	++	?	+	+	+	+	—	—	Arteriosclerotic heart disease; auricular fibrillation.
14	75	M	left	6 days	?	+	?	+	+	+	+	—	—	Femoral vein thrombosis.
17	53	M	right	14 days	(c)	++	+	—	—	—	(b)	—	—	Mural thrombus; left ventricle myocardial infarct.

(a) Compression of anterior cerebral by falx (herniation) caused distal anterior cerebral distribution softening.
(b) Cortex and cortico-medullary junction.
(c) Both posterior communicatings small; left smaller than right.
N=Normal.

The patients varied from 23 to 75 years of age. All but five cases were in the sixth, seventh, and eighth decades. There were 13 female and eight male patients. Clinically, hypertension was present in seven patients, all of whom were over 55 years of age, but in no way could this hypertension be correlated with the pathologic picture. The time interval from clinical evidence of occlusion to death varied from 21 hours to 46 months.

The internal carotid artery was occluded on one side, either in the neck or in its intracranial portion, with the exception of one case (case 4) in which there was bilateral occlusion in the siphons, and one case (case 16) in which the common carotid was occluded from its origin in the aorta to the bifurcation. The right internal carotid was occluded in seven specimens, the left in 12. Aneurysms were present in eight circles of Willis, contributing to the high incidence of post-ligation specimens. In addition, carotid arteriovenous fistula, present in case 13, was treated by ligation of the internal carotid artery.

CAUSE OF OCCLUSION

In the accompanying tables the cases have been collated on the basis of cause of the vascular occlusion. The cause was demonstrable or justifiably surmised in all but three patients.

In five cases "spontaneous" or arteriosclerotic thrombosis was the cause of the occlusion (table 1). These patients, ranging from 55 to 73 years of age, survived from 21 hours to 46 months after the onset of symptoms. In case 16 there was an occlusion of the left common carotid artery from its origin at the aorta to the bifurcation, with no evidence of clot in the intracranial portions. Patency of the internal carotid in the neck was not evaluated in three specimens (cases 8, 19, and 21). The carotid siphon and proximal portion of the middle cerebral arteries contained an ante mortem thrombus in four specimens, one of which (case 1) had thrombosis of the internal carotid within the neck. Variations in the anatomy of the circle of Willis were present in all four of the circles where descriptions were available. These anomalies were small posterior communicating vessels on the side of occlusion in cases 1 and 19, and in case 8 consisted of bilateral stringlike posterior communicating vessels with the anterior communicating artery also of minute caliber. The fourth anomaly (case 16) represented a perpetuation of the embryologic status in which the posterior cerebral vessel derives directly from the internal carotid artery. The prominence of arteriosclerosis of the circle of Willis in this group was in marked contrast to the remainder of the series.

Embolic occlusion was found in five cases (table 2). The heart was the source of the embolus in four of these and a femoral vein thrombus in the other. Auricular fibrillation in either rheumatic or arteriosclerotic heart disease was present clinically before death in three of the cardiac cases and an old mural thrombus secondary to a myocardial infarct of the left ventricle in the other. Other viscera showed embolic lesions in each case. The survival period varied from two to 14 days in these patients. Despite the age range from 53 years to 75 years, arteriosclerotic changes in the circle of Willis were less prominent than in the spontaneous group. In only two cases were sufficiently complete anatomic descriptions of the circle of Willis

TABLE 3

INTERNAL CAROTID OCCLUSION

LIGATION FOR ANEURYSM

Case	Age	Sex	Side	Survival after Occlusion	Circle of Willis: Anatomic Variations	Circle of Willis: Arterio-sclerosis	Site of Occlusion: Neck	Site of Occlusion: Siphon	Site of Occlusion: Middle Cerebral	Site of Occlusion: Anterior Cerebral	Pathologic Lesions: Middle Cerebral	Pathologic Lesions: Anterior Cerebral	Pathologic Lesions: Posterior Cerebral
2	68	F	right	1 day	(a)	+++	+	+	—	—	+	—	—
3	51	F	left	2½ days	(b)	—	+	—	—	—	+	—	—
9	45	F	left	2½ days	N	—	—	+	—	—	+	—	—
11	64	F	left	3 days	(c)	+	—	+	—	—	—	—	—
13	61	M	left	5½ days	N	+	+	—	—	—	+	—	—
15	66	F	right	12 days	?	—	+	+	—	—	+	—	—
20	59	F	left	43 months	(d)	+++	—	+	—	—	—	—	—

(a) Anterior communicating small; right posterior communicating stringlike and occluded.
(b) Left posterior communicating stringlike.
(c) Anterior communicating stringlike.
(d) Posterior communicating small, bilaterally.
N=Normal.

TABLE 4

INTERNAL CAROTID OCCLUSION

UNKNOWN SOURCE

Case	Age	Sex	Side	Survival after Occlusion	Circle of Willis: Anatomic Variations	Circle of Willis: Arterio-sclerosis	Site of Occlusion: Neck	Site of Occlusion: Siphon	Site of Occlusion: Middle Cerebral	Site of Occlusion: Anterior Cerebral	Pathologic Lesions: Middle Cerebral	Pathologic Lesions: Anterior Cerebral	Pathologic Lesions: Posterior Cerebral	Remarks
4	47	F	left and right	1½ days	N	+	?	+	+	—	—	—	—	? Edema, then thrombosis.
10	24	F	left	3 days	?	—	+	+	+	—	+	—	—	? Ligated.
18	48	F	left	8–9 weeks	(a)	+	—	+	—	—	+	—	—	? Edema, then thrombosis.
						Occlusion Following Angiography								
6	23	M	right	2 days	(b)	—	(c)	—	—	—	+	—	—	Repeated injections.

(a) Left posterior communicating larger than right (see case report).
(b) Right carotid much smaller than left.
(c) Injected at autopsy table and "patent," not examined.

available. One of these (case 12) had a normal configuration. The circle in case 17 had small posterior communicating vessels on either side. The anterior cerebral artery was occluded by propagated clot in three specimens (cases 7, 12, and 14), as well as the middle cerebral artery and the intracranial portion of the internal carotid. In case 5 the internal carotid siphon and proximal portion of the middle cerebral artery were occluded, whereas in case 17 the intracranial vessels were patent but the internal carotid was occluded within the neck. The neck vessels were not examined at the autopsy table in the remaining cases.

In seven cases *ligation of the internal carotid artery* either in the neck (cases 2, 3, 13, and 15) or in the intracranial portion of the carotid (cases 9, 11, and 20) accounted for the occluded vessel (table 3). The period of survival varied from one day to 43 months after ligation. Although the patients varied from 45 to 68 years of age, the average age (59 years) was only slightly younger than that of the former groups. A significant degree of arteriosclerosis in the circle of Willis occurred in only two specimens (cases 2 and 20). The circles of Willis were anatomically normal in two specimens and not described in one. Of the four remaining circles, the posterior communicating vessels were stringlike on the side of the lesion in three, in one of which (case 2) the anterior communicating artery was also small. The anterior communicating artery was abnormally small in the fourth. In no case was there an extension of thrombus into either the middle cerebral or the anterior cerebral artery.

The internal carotid occlusion was directly related to *angiography* in one case (case 6) (table 4). This patient suffered immediate symptoms during injection of the radiopaque material. There was no thrombus in the intracranial portion of the internal carotid artery. The diameter of the involved vessel was one-half that of its mate. Although resistance to flow within the carotid in the neck was demonstrated at the autopsy table, no definite occlusion was found.

In the remaining three cases the cause was *unknown* (cases 4, 10, and 18) (table 4). In case 4 ante mortem clots were found in both internal carotid vessels at autopsy. Both hemispheres of the brain were markedly edematous, no significant atheromatous degeneration of the vessels was found, and no source of emboli or evidence of fat emboli was noted. The possibility was entertained but not proved that secondary thrombosis was consequent to cerebral edema, associated with surgery for the reduction of a malleolar fracture. In case 10 the patient, who had symptoms of an internal carotid aneurysm, underwent angiography and surgical exploration. No aneurysm was found. The patient died three days after surgery and an ante mortem thrombus was present in the internal carotid artery in the neck and in its intracranial portion, extending into the middle cerebral artery. Case 18, in whom multiple possible causes occurred, is more fully described below.

In no case in this series could evidence of arteritis be discovered, nor could syphilis be indicted.

GROSS PATHOLOGY

With three outstanding exceptions (cases 4, 11, and 20), the gross pathologic damage was found in the distribution of the middle cerebral artery on the side of the occluded internal carotid

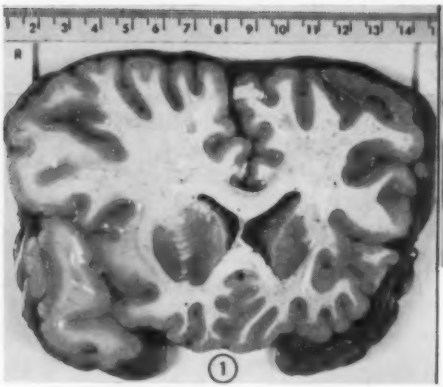


FIG. 1. *Case 6.* Functional occlusion of right internal carotid artery during angiography. Survival period two days. There is pronounced swelling of the right hemisphere, with shift of midline structures to the left and herniation of the gyrus rectus under the falx.

FIG. 2. *Case 14.* Embolic occlusion of left internal carotid artery. Survival six days. There is destruction of tissue in the territory of the middle cerebral artery.

vessel (figures 1, 2, 3, and 4). It was not simply extension of the thrombus into the middle cerebral artery which accounted for this picture, for in eight cases no evidence of propagation of a clot into the middle cerebral vessel itself could be found.

Occlusion of the anterior cerebral artery by the propagated thrombus in one of three cases (case 8) resulted in softening in the distribution of this vessel also. In the only other case where the anterior cerebral distribution was involved (case 7), a herniation of the gyrus cinguli occurred under the falx. This herniation was secondary to edema of the hemisphere on the involved side and caused occlusion of the terminal portion of the anterior cerebral artery. This mechanism failed to result in anterior cerebral involvement in all instances, for in a similar specimen (case 10) no anterior cerebral involvement was found. No sign of encephalomalacia in the distribution of the posterior cerebral artery was noted in any case.

Of no little interest are the two instances in which no evidence was found of gross or microscopic damage to the brain (cases 11 and 20). In case 4 no gross pathologic lesions aside from edema could be demonstrated, although scattered foci of cell loss were present and there was an increase in the prominence of cortical capillaries, indicative of hypoxia.

Pontine hemorrhages, usually in the midline and scattered occasionally through the anterior portion of the tegmentum, were a frequent accompaniment of the cerebral infarcts in the cases of shorter duration, up to 12 days after occlusion. This phenomenon was invariably associated with gross edema or swelling of the involved hemisphere and with herniation and necrosis of the uncus on that side. That it was not, however, an invariable occurrence with gross brain swelling is noted from the following: there were 12 specimens with frank brain swelling on the affected side; ten of these showed uncal herniation and necrosis; of these, only six demonstrated pontine hemorrhages.

An attempt at estimating the degree of atheromatous degeneration of the ves-

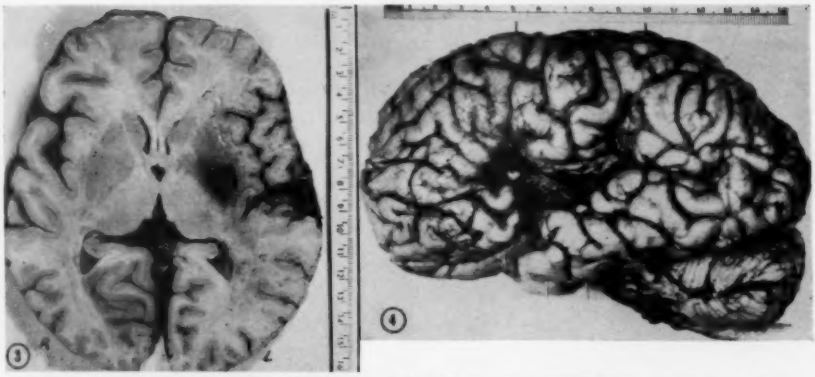


FIG. 3. *Case 16.* Arteriosclerotic thrombosis of the left common carotid artery. Survival 13 days. Softening in the distribution of the middle cerebral artery on the left, with more recent hemorrhagic necrosis of the caudal portion of the left putamen.

FIG. 4. *Case 21.* Old scar formation in the left hemisphere, principally in the insular region. Survival 46 months.

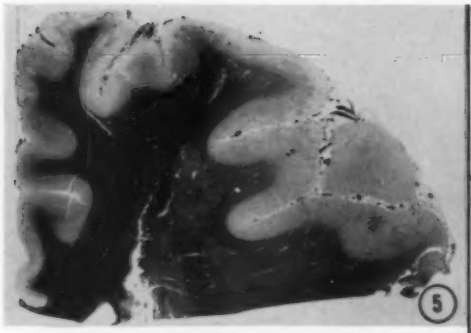
sels of the circle of Willis was made.* The only apparent correlation between the degree of arteriosclerosis of the component vessels of the circle of Willis occurred in those cases of "spontaneous" occlusion. Nor could age be correlated with degree of atheromatous degeneration. Although the five patients with marked (+++) to severe (++++) arteriosclerosis were over 55 years of age, nine patients over this age were rated none to moderate (++) in degree.

Anomalies of the circle of Willis which might be of significance (aside from aneurysms) occurred in seven of the 14 circles in which adequate descriptions were available. These anomalies were either stringlike (diameter of less than 1 mm.) posterior communicating vessels on one or both sides, similar small anterior communicating arteries, or a combination of these. In two cases there was inequality of the size of the posterior communicating arteries, the smaller vessel being on the side of the occlusion. The circle of Willis was completely normal in four instances, whereas six circles were inadequately described. In two cases, one of which had a stringlike posterior communicating on the side of the lesion, a persistent embryonic anomaly was present where the posterior cerebral vessels arose directly from the internal carotid artery.

*(+) indicated an occasional plaque, usually at the bifurcation of the various branches, with no significant encroachment upon the lumen. (++) indicated more evident plaques, with mild encroachment on the lumen or with pipestem vessels which failed to collapse normally and appeared to have lost much of their elasticity. (+++); from one-fourth to two-thirds of the lumen was encroached upon by atheromatous plaques. (++++): one-third or less of the lumen was available for the transit of blood. These were gross estimates only.

HISTOPATHOLOGY

As one might surmise, the microscopic picture of the involved areas varied with the time interval from the occlusion (figures 5 and 6). In no way did it differ from the results of vascular occlusions of similar duration from any cause. There was no sharp dividing line between normal and softened tissue any more than in occlusions of other major vessels. Hemorrhagic infarcts, either in the lenticulostriate area or at those junc-



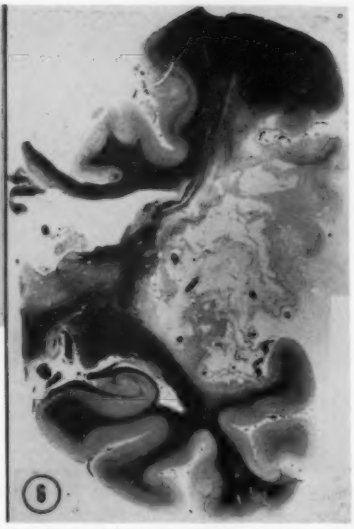


FIG. 5. *Case 13.* Coronal section of left superior frontal cortex and centrum, celloidin section stained by Weil method. Survival five and one-half days. There is a pallor of staining in the territory of the middle cerebral artery, with geographic involvement of the junctional area between anterior and middle cerebral artery territory of distribution.

FIG. 6. *Case 21.* Survival period 46 months. Weil-stained celloidin section of the cystic scarred area seen in figure 4. The encephalomalacia is limited to the territory of the left middle cerebral artery, with complete destruction and replacement by cystic gliosis.

tional areas between the middle cerebral and either the posterior or anterior arteries, occurred with no regular pattern. No definite intravascular microscopic evidence of embolic thrombi occurred, even in those cases in which embolism was indicted as a cause of the carotid occlusion. Small, older infarcts, however, occurred in several of the embolism cases.

There was no histologic evidence in any instance that the thrombus originated in the distal termination of the vascular tree, extending down into the internal carotid artery. The opposite condition, or distal propagation of the thrombus, was apparent in several specimens.

There was one patient (case 19) who gave the clinical history of a progressive steplike lesion occurring over a period of two and one-half months. At autopsy, older areas of softening were present in the middle cerebral artery supply at its junctions with the posterior and anterior artery distributions. The remainder of the area of supply of the middle cerebral artery showed softening compatible with the seven-day interval since the last "attack."

DISCUSSION

Since the literature dealing with the clinical and pathologic features of internal carotid thrombosis has been extensively reviewed in several recent publications, no effort will be made to reiterate this material. Particularly noteworthy are the papers by Fisher,[1,2] Gurdjian and Webster,[3] and Maspes and Fasano.[4] The monograph by Avet[5] contains not only a remarkably complete critical bibliography of the anatomy of the circle of Willis, but also a provocative review of various mechanisms involved in the pathogenesis of the lesions incident to

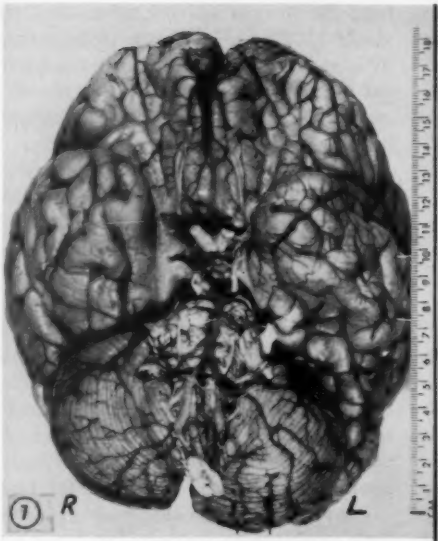


FIG. 7. *Case 6.* Survival two days. The right hemisphere is swollen, and herniation of the right uncus has resulted in necrosis. The defect at the apex of the herniated uncus is an artefact of this necrosis.

FIG. 8. *Case 7.* Survival two and one-fourth days. The severe edema following embolic occlusion of the left internal carotid artery has resulted in herniation of the gyrus rectus under the falx, with secondary involvement of the anterior cerebral territory and hemorrhagic infarction. There are associated pontine hemorrhages. There are several small older areas of softening with scar formation in the right hemisphere.

ligation of the internal carotid artery. In essence, Avet divides the potentially significant features of the physiopathology of carotid ligation into five categories. These are: 1) acute ischemia consequent to insufficiency of the circle of Willis; 2) thrombosis following the ligation; 3) embolism from such a thrombosis; 4) sympathetic vasomotor mechanisms and reflexes from the carotid sinus; and 5) secondary factors inherent to the total illness of the patient and his general circulation, such as blood volume, blood pressure, age, and degree of arteriosclerosis.

In the 21 cases constituting the material of the present report, not only were there varied pathologic features, but there appeared to be a variable pathogenesis for the lesions encountered.

The outstanding feature observed in the present series was the limitation of the gross pathologic alterations, predominantly to the distribution of the middle cerebral artery. This phenomenon has been observed by others.[1,4,6–9] Other areas also were involved in certain cases, but these were the result of independent factors of various sorts. Such included small, ancient, presumably embolic softenings, or lesions resulting from previous surgical trauma consequent to ligation of an aneurysm. The actual propagation of the clot into the anterior

cerebral artery resulted in softening in the distribution of this vessel, but occurred in only one of three such instances. Brain swelling and consequent herniation of the gyrus cinguli under the falx or of the uncus beneath the tentorium were further factors accounting for secondary lesions in some instances (figures 7 and 8). Under the latter circumstances, fresh pontine hemorrhages were likely to be encountered.

We can only speculate as to the cause of this middle cerebral localization of the grossly affected tissue. In some instances, the actual extension of a thrombus into the proximal portion of the middle cerebral artery would account for the distribution of the softening. Such occurred in ten of the 21 specimens. Under these circumstances, the question must be answered as to why the territory of the anterior cerebral artery was not also involved.

In the many cases where there was no clot in the middle cerebral artery, other factors must be indicted. It would seem that the direct linear extension of the lumen of the internal carotid into the middle cerebral artery should be a factor in the localization to the field of supply of the latter vessel. Certainly if emboli were dislodged from the main occlusion in the internal carotid artery, these could most easily be directed into the middle cerebral lumen because of such direct extension. In the present series, no pathologic evidence of such a process could be demonstrated. Furthermore, involvement of the basal ganglia, especially the striate body, indicated that the proximal branches of the middle cerebral artery were implicated in the ischemic process. That an embolus was not dislodged to occlude these proximal branches would seem plausible from the observation that, while the striate body showed evidence of softening in 16 cases, there was an occlusion present in the promixal part of the middle cerebral artery or its lenticulostriate branches in only ten cases.

The possibility of spasm of the middle cerebral artery secondary to the sudden mechanical stimulation of either an embolus, ligation, or the irritation of angiography is a possibility which cannot be disproved,[10,11] and our case 6 possibly fits into this category.

It is conceivable that a thrombus in the more distal branches of the middle cerebral artery could, by retrograde extension of the clotting process, build up sufficiently while passing downstream toward the circle to occlude the internal carotid artery. We could find no histologic evidence to support this hypothesis and, in fact, found the opposite indication, with the younger appearing clot distal to the internal carotid.

If the distal branches of the middle cerebral artery were more susceptible to a drop in blood pressure than those of the other major vessels as a result of occlusion of the internal carotid artery, a major factor in the localization of the softening process would be present. The gradient of blood pressure in the cerebral vessels of the human has recently been recorded by Sweet and his co-workers[12–14] and others.[15] But this drop has not been limited to the middle cerebral territory, for a similar fall occurred in the branches of the anterior cerebral artery.[14] Thus, the anatomic feature of the direct continuation of the middle cerebral artery from the internal carotid cannot be the sole cause of the demonstrated pathologic distribution.

Another important and obvious anatomic factor is the potential anastomosis

in the circle of Willis between the carotid circulations on either side and the vertebral-basilar circulation.

In the functionally normal circle of Willis, the vertebral circulation supplies the posterior cerebral territory and no interference would be expected from an occlusion of the internal carotid artery. In an emergency, with adequate posterior communicating vessels, collateral supply could be established in the distribution of the middle cerebral artery from this source. That such actually happens can be illustrated perhaps by case 18. In this patient an aneurysm of the anterior communicating artery showed clinical signs of rupture, and during the initial ictus the patient was unable to move her right leg for five hours. Three days later she was slightly incoherent and disoriented, had grossly bloody cerebrospinal fluid, but no obvious hemiparesis. For the four succeeding days she was given heavy doses of opiates. On the seventh day after onset a right hemiparesis occurred. The patient entered the hospital nine days after onset, at which time she showed a right hemiparesis, was stuporous, and had a mildly xanthochromic spinal fluid. Angiography on the following day showed a constriction of the left internal carotid artery, but no aneurysm was found. Three weeks after her initial episode, clinical evidence of a second leakage occurred. After a variable and fluctuating course, left-sided motor seizures suddenly developed ten weeks subsequent to her initial hemorrhage, she became cyanotic and expired. At autopsy an aneurysm of the anterior communicating artery with old and recent subarachnoid hemorrhage was found. Within the calvarium, the left internal carotid artery showed an old organized fibrous thrombus which did not extend beyond the left posterior communicating artery. The cortex of the left Sylvian fissure showed a laminar type of necrosis several weeks old (figure 9). A similar but minute lesion was demonstrable in the posterior angle of the Sylvian fissure on the right. Examination of the circle of Willis showed the lumen of the anterior communicating artery obliterated with clotted blood and a laminated thrombus within the aneurysm. The right posterior communicating artery was duplicated. On the left side there was a larger than normal posterior communicating artery which gave reason to believe that a good potential anastomosis was present between the vertebral-posterior cerebral and the middle cerebral arteries beyond the point of occlusion by the carotid thrombus. It is presumed that ischemic, laminar damage to the left Sylvian cortex occurred at the time of the occlusion, but that collateral supply through the vertebral system occurred sufficiently soon after this occlusion to forestall necrosis of the entire middle cerebral artery territory.

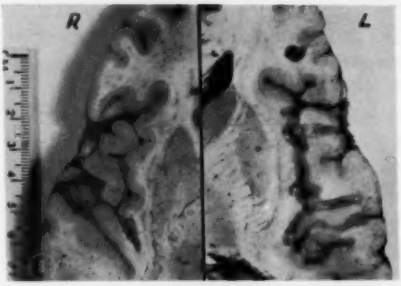


FIG. 9. *Case 18.* Survival eight or nine weeks. Laminar necrosis of the left insular cortex sparing much of the distribution of the middle cerebral artery, possibly because of exceptional collateral supply. Old thrombus of the left internal carotid artery was limited to the siphon. The minute lesion in the right sylvian fissure at its posterior end is not explained.

The other possible sources of collateral circulation are first, from the opposite internal carotid branches by means of the anterior communicating artery, and second, from the homolateral external carotid by reverse flow in the ophthalmic artery to the internal carotid above the point of occlusion.[16] The latter of these two can, of course, be of little value when the thrombus extends within the siphon. The third possibility, the potential significance of meningeal artery anastomoses, has been emphasized recently by vanderEecken and Adams.[17] It is by means of anastomosis through the anterior communicating vessel that the anterior cerebral territory was spared in some instances.

Although the significance of an anomalous circle of Willis is speculative at the present time, it would seem plausible that a functionally imperfect circle, that is, one with attenuated or stringlike anterior or posterior communicating vessels, could contribute to the devastation of an occlusion of the internal carotid artery.

Even with collateral sources of blood supply available from the anatomic viewpoint, arteriosclerotic narrowing of the lumen of the anastomotic vessels would diminish the efficiency of these collaterals. In many of the cases recorded in the literature,[1,5] as well as several in the present series, especially in the first two groups (tables 1 and 2), this arteriosclerotic factor is important. Sweet and Bakay[14] consider that it is not alone the size of the main branches which is significant, but the sum of the cross sectional areas of and lengths of the anastomozing vessels. There again, arteriosclerotic narrowing would contribute to diminished function.

The practical value of what might be called the mechanical or anatomic features of collateral circulation through anastomotic channels of the circle of Willis and the added significance of arteriosclerotic narrowing of the component vessels cannot explain all of the cases, nor the entire picture in every case. Other physiologic features must be at play. Such can be divided roughly (and artificially) into those compensatory reflexes which tend to preserve the hemodynamics or homeostasis of the cerebral circulation, and extracranial, systemic processes which can be reflected in cerebral physiopathology.

The presence of brain swelling in the early course of the pathologic process is a well recognized consequence of the sudden occlusion of a vessel within the brain. The basic factor at work is the ischemia or localized hypoxia resulting from the loss of blood supply. The exact mechanism by which interstitial fluid is accumulated is more difficult to explain. In addition to vasodilation and carbon dioxide accumulation, a presumed increase in permeability of the capillary vessels, plus venous engorgement and poor drainage from the field of supply, are factors of significance. Some degree of collateral circulation must also occur to allow for an increase in the circulating fluid in the infarcted area. That a vicious cycle of self perpetuation occurs seems obvious. Not only is there a hemodynamic shift, but also poor venous drainage occurs from diffuse compression, as well as focal compression under such localized structures as the falx or the tentorium. The systemic circulation responds by a rise in systolic blood pressure in the usual case[16,18] and, given an adequate collateral circulation with vascular structures not further compromised by arteriosclerosis, focal damage

or none at all is to be expected.

It might be added that the clinical feature of headache, not uncommon in cases of spontaneous occlusion of the internal carotid, can be explained not only on the basis of compensatory dilation of the major vessels, as Willis first suggested,[16] but also by this edema which is such a fairly constant feature in the early stage of the occlusion. Under the latter circumstances, the shift against the tentorium or other dural reduplications would cause head pain.

Brackett[18] further suggests a plausible explanation for the ischemic results which can complicate this edema. The physiologic blood pressure of the terminal carotid circulation exists at a somewhat lower level than the proximal pressure.

It is Brackett's hypothesis that the terminal pressure may be so reduced by the ligation (or occlusion) of the internal carotid artery that it cannot exceed the increased intracranial pressure and ischemic sequelae result. Sweet and coworkers[14] have found a marked variability in the drop in intracerebral blood pressure on occlusion of the internal carotid artery, not only among different patients, but, in at least one case, between two different readings in the same patient after an interval of several days. Another feature which might tend to perpetuate damage is the increased cerebrovascular resistance found by Shenken[19] after ligation of the internal carotid artery. In general, the compensatory systemic hypertension which occurs tends to overcome these hemodynamic effects but if systemic hypotension is present because of shock, surgical trauma, myocardial disease, hemorrhage, or other processes,[1,9] such compensatory increase may not be effective.

Whether the factor of age itself is significant in the disastrous effects of internal carotid occlusion is a moot question. Certainly the margin of safety present in any of the above factors would probably be diminished, especially when age and arteriosclerosis are combined.[8,13]

Manipulation in the region of the carotid sinus from attempts at angiography or ligation or trauma from emboli suddenly occluding the region of the sinus not only can result in prolonged spasm of the internal carotid,[8,10,11] but, by precipitating a vagal depressor reflex,[20] induce systemic hypotension which will increase the hazards of carotid occlusion. Each factor must be weighed separately in the individual case. In general, the carotid sinus mechanisms are more significant in the complications of surgical ligation than in spontaneous occlusion.

Of some interest are the three cases which had no gross evidence of softening after occlusion of the internal carotid. In case 4, who succumbed only one and a half days after thrombosis of both carotids, there may have been insufficient time for the pathologic picture of softening to develop. Microscopically, occasional cell changes indicative of hypoxia were noted, especially at the base of gyri, but aside from uncal herniation with necrosis and fresh pontine hemorrhages, no other significant lesions were present. In case 11 the internal carotid artery was ligated for an intracranial aneurysm. The patient, a 64 year old hypertensive female, failed to regain consciousness and died three days after operation, presumably from myocardial insufficiency. No gross or remarkable microscopic abnormalities of the brain were present. There was mini-

mal arteriosclerosis of the circle; the anterior communicating artery was stringlike. Case 20, a 59 year old female with no hypertension, died 43 months after intracranial ligation of the internal carotid. The only abnormality noted was a small, old lesion of the gyrus rectus, presumably contusion from surgery. There was fairly marked arteriosclerosis of the circle. The posterior communicating vessels on either side were small, but the anterior cerebral arteries on both sides and the anterior communicating artery were larger than normal, suggesting a possible adequate collateral circulation from the patent side.

Neither anomalies of the circle of Willis nor arteriosclerosis can be a sufficient cause to explain more than certain individual cases. The diversity of findings, varying as they do from case to case, is an indication that the same mechanism may not be involved in every case. Other factors, including the status of the systemic circulation and of cerebral metabolism,[21] must be evaluated in each individual patient.

From the clinical evidence that occlusion of the internal carotid can be safely accomplished, and from the lack of cerebral pathology in occasional cases, it is safe to assume that some mechanism for collateral circulation exists within the brain. From our analysis and that of others, this compensatory mechanism is not identical in every case.

Only continued investigation may give us the answer. We can only agree with Fisher that an awareness of the possibility of internal carotid occlusion and a consequent search at the autopsy table will help to explain certain heretofore unexplained softenings, especially in the distribution of the middle cerebral artery. An analysis of the functional anatomy of the circle of Willis may then add a hint as to the mechanism involved.

SUMMARY AND CONCLUSIONS

In a series of 21 autopsy specimens in which occlusion of the internal carotid artery had occurred, the causes of occlusion were "spontaneous" or arteriosclerotic in five cases, embolism in five cases, surgical ligation, usually for aneurysm, in seven cases, and unknown in three cases. In addition, one occlusion occurred at the time of angiography. The patients survived for periods varying from 21 hours to 46 months after the occlusion. All except three specimens had cerebral softening in the territory of the middle cerebral artery on the side of the occluded internal carotid vessel. The area of distribution of the anterior cerebral artery was involved in one of these specimens. In three cases no gross or microscopic evidence of encephalomalacia was found. Significant swelling of the affected hemisphere occurred in the acute cases up to 12 days after the ictus. Anomalies of the circle of Willis in the form of attenuated anterior or posterior communicating vessels, which limit the functional anastomosis of this arterial circle in times of emergency, especially when the vascular lumens are embarrassed by arteriosclerosis, appear to have significance in the development of cerebral pathology in some cases. Other probable factors are discussed which, alone or in combination, will influence the extent and location of the encephalomalacia.

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■ With respect to the causes of *Hemiplegia*, I wish to remark that they are more especially those of apoplexy. Palsy in this form is almost always preceded by an apoplectic fit, of greater or less duration and violence; the causes, therefore, of both are similar. Hemiplegia may indeed be occasioned directly, and without the intervention of apoplexy; as by injuries done to the head from falls and blows, but cases of this kind very seldom occur. The causes of these diseases, when they act generally and powerfully, seem to produce apoplexy, and to give occasion to palsy when they act partially, or with less violence; so that, by an increase of power of the cause, palsy may terminate in apoplexy; and by a diminution of it, apoplexy may terminate in palsy. Dr. Cullen says, "the compression occasioning hemiplegia may be of the same kind, and of all the different kinds that produce apoplexy; and therefore either from tumour, over-distension, or effusion:" and almost all who have written on these diseases agree in opinion with Dr. Cullen on this subject.

John Cooke in *A Treatise on Nervous Diseases*, pubilshed in 1824.

Central Nervous System in Carbon Tetrachloride Intoxication

Maynard M. Cohen, M.D.

THE EARLIEST and often most severe manifestations of carbon tetrachloride poisoning are those of nervous system involvement. They include headache, vertigo, ataxia, weakness, visual blurring, and lethargy progressing to coma. As the intoxication continues, pareses, tremors, convulsions, confusion, disorientation, impaired mentation, optic neuritis, or polyneuritis may appear.[1–3] Evidence of hepatic and renal involvement generally follows the early neurologic symptomatology, then often dominates the clinical picture. Numerous investigations have established the nature and severity of the liver and kidney damage,[4–8] and others have indicated cardiac,[9] pulmonary,[4,10–12] pancreatic,[13] gastrointestinal,[14] and hematopoietic[15] pathology. In contrast, neuropathologic studies of carbon tetrachloride intoxication have been so meager as to preclude the establishment of any characteristic picture. Thus the pathogenesis of the neural lesions remains to be clarified.

The most detailed analysis of the neural changes was reported by Stevens and Forster in 1953.[2] However, the neuropathologic examination was available in only two of their 15 clinical cases. The first of these cases exhibited localized areas of demyelination, necrosis, and phagocytosis in the cerebral white matter, together with occasional glial nodules. The histologic abnormalities in the second case were cerebellar, with disorganization of the molecular layer and falling out of neuronal elements. The Purkinje cells were decreased in number and the remaining cells were pyknotic.

Scattered experimental studies have demonstrated other neuropathologic changes. Biancalini[16] reported neuronal swelling, chromatolysis or pyknosis, neuronophagia, perivascular astrocytic proliferation, and acute oligodendroglial swelling following acute or chronic carbon tetrachloride poisoning in dogs and rabbits. Fresh cerebellar hemorrhages were noted by Tanohata and Tagawa[17] in experimental canine intoxication. Purkinje cells were decreased in numbers and were pale or cyanotic. Neuronal alterations were observed in the nuclei of Goll and Burdach, and perivascular glial proliferation was present in the cerebral white matter.

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Ferroni and Bernardini[18] could not substantiate significant neuronal changes in rats administered carbon tetrachloride twice weekly over a 50-day period. They did note yellow-orange droplets in clusters of 10 to 30 associated with myelin sheaths or blood vessels.

The two cases of carbon tetrachloride intoxication in the present report exhibited striking nervous system pathology which appeared valuable in clarifying the nature and genesis of the neural changes.

CASE REPORTS

Case 1. A 24 year old white male was admitted to the Minneapolis Veterans Administration Hospital January 25, 1955, shortly after ingesting three-quarters of a bottle of Energine cleaning fluid (75 per cent carbon tetrachloride, 25 per cent naphtha) in a suicidal attempt. He had vomited five times and had had three episodes of diarrhea following ingestion of the solution, but complained only of slight nausea at the time of admission. Questioning revealed a history of alcohol consumption of one to two pints of whiskey weekly for over one year and one pint was consumed the night prior to his attempted suicide. He frequently smoked marihuana and ingested dexedrine or benzedrine. His medical history also included an episode of acute hepatitis with jaundice in 1953, as well as prior hospitalization for psychiatric difficulties.

The admission physical examination revealed a well developed white male with a noticeable odor of carbon tetrachloride to his breath. There was conjunctival and pharyngeal infection and slight epigastric tenderness. No other abnormality was noted and the abdominal viscera were not palpable.

Laboratory studies. Admission urinalysis revealed a clear amber urine with a specific gravity of 1.026, a trace of albumin, and occasional white cells in each high powered field. During the remainder of hospitalization the urinary albumin then varied between 2 and 4 plus. Granular casts and red blood cells appeared in the urine on February 1. Hematologic examination on admission revealed 19,050 white cells, with a differential count of 86 per cent neutrophils, 13 per cent lymphocytes, and 1 per cent eosinophils. The hemoglobin was 15 gm. per cent and the sedimentation rate 2 mm. per hour on January 25. The hemoglobin level gradually fell to reach a low of 8.2 gm. on February 7. The platelet count was 182,000 per cu. mm. on January 28. The bleeding time was two minutes with a clotting time of 21 minutes on February 2. The bleeding time then rose to over eight minutes on February 7. At that time clot retraction required 12½ minutes and retraction was good in one hour. Blood serology was negative.

The blood urea nitrogen level gradually rose from 16 mg. per cent on admission to 389 mg. per cent on February 6. The blood carbon dioxide combining power fell from 22 mEq./L. on January 26 to 9.9 mEq./L. on February 2. The serum chlorides were lowered from 102.9 mEq./L. on January 26 to 80 mEq./L. on February 2. The blood sodium varied from 138.4 to 144.7 mEq./L. The blood potassium level rose from 4.1 mEq./L. on January 26 to 7.7 mEq./L. on February 6.

Other blood chemistry examinations on February 2 revealed an alkaline phosphatase of 10 King-Armstrong units, fasting blood sugar of 85 mg. per cent, calcium of 8.5 mg. per cent, and inorganic phosphorus of 12.6 mg. per cent. A bilirubin determination on January 26 was recorded as 1.1 mg. per cent at one minute with a total of 4.8 mg. per cent, and rose to a high of 4.6 mg. per cent at one minute with a total of 9.1 mg. per cent on January 28. The thymol turbidity was 6.4 units on January 27, while the cephalin flocculation varied between 1 and 3 plus in 24 hours. The prothrombin time varied from 12 to 36 per cent of normal.

Hospital course. Urinary excretion fell from a volume of 500 cc. on the night of admission to 275 cc. over the next 24 hours. Complete anuria ensued on the third day and during the subsequent hospitalization the daily urinary volume never exceeded 100 cc. Methionine, together with 10 per cent glucose in water, was administered on the second hospital day. Grand mal seizures appeared on the eighth day of hospitalization and were controlled with sodium Amytal and Dilantin. Tracheotomy was performed on the same day. In the following days bleeding occurred from the gastrointestinal tract as well as from the area surrounding the tracheotomy tube. Deterioration was pro-

gressive and death ensued on the thirteenth day following admission.

Postmortem examination. The principal pathologic alterations were limited to the nervous system, liver, kidneys, and gastrointestinal tract.

External examination of the brain revealed an unruptured aneurysm measuring 0.6 cm. in diameter at the junction of the left anterior cerebral artery with the anterior communicating artery. Proximal to this aneurysm the diameter of the right anterior cerebral artery was approximately three times that of the left. On section three discrete hemorrhagic areas were present bilaterally in the cortex of the posterior lobe of the cerebellum. These areas varied from 0.3 to 0.8 cm. in maximum diameter.

Microscopic examination of the brain was carried out employing hematoxylin and eosin, Nissl, Weil, gallocyanin, azo-carmine, Sudan IV, and Mallory phosphotungstic acid stains. The blood vessels were congested throughout. The arachnoid overlying the grossly hemorrhagic areas in the cerebellum was thickened and infiltrated by small numbers of mononuclear leukocytes, as well as occasional phagocytes containing light brown pigment. The subarachnoid space contained extravasated red blood cells. The cerebellar hemorrhages were present in two patterns. In the first (figure 1) there was a centrally located dilated thin-walled vein whose lumen was filled with a thrombus consisting of red blood cells, fibrin strands, and aggregates of mononuclear and polymorphonuclear leukocytes. Small numbers of neutrophils were also present within the wall of the vein. Red blood cells were extravasated about the thrombosed vessel involving both the granular and molecular layers of the cerebellum. About the hemorrhage the cerebellum exhibited demyelination. Adjacent to the hemorrhagic area there was a "status spongiosus," with the granular layer widely separated from the molecular layer by somewhat loculated spaces suggestive of an edematous appearance. The Purkinje cells were diminished in number in this area and many of the remaining cells exhibited swelling and chromatolysis. In some cells this alteration progressed to ghost cell formation. Other Purkinje cells in the same area exhibited shrinkage, pyknosis, and tortuosity of their processes. Many Purkinje cells appeared to be displaced into the molecular layer. Occasional capillaries adjacent to the Purkinje cell alterations exhibited endothelial proliferation. Although the edematous appearance and Purkinje cell alterations were most prominent in the regions of hemorrhage, similar changes were also evident in areas distant from any extravasation of blood (figure 2).

The second pattern of hemorrhage in the cerebellum was in the form of small extravasations of blood scattered throughout the cortex in the distribution of a hemorrhagic infarct (figure 3). The hemorrhages were most prominent in the molecular layer, but there was some extension into the underlying granular layer and cerebellar white matter. Occasional fat granule cells were present at the junction of granular and molecular layers.

Examination of the cerebral hemispheres revealed occasional small perivascular areas of demyelination containing moderate numbers of pigment-containing phagocytes. Within the brain occasional swollen and chromatolytic neurons were present in the dorsal motor nucleus of the vagus and the lateral cuneate nucleus. Occasional petechiae were also present in the floor of the fourth ventricle and in the ventral pons.

The principal alterations in the remainder of the autopsy examination included central necrosis of the hepatic lobules, degeneration of renal tubules, and extravasation of blood into the submucosa of small intestine and the periadrenal fat.

Case 2. A 40 year old white male had been a "heavy drinker" for several years prior to hospitalization. On April 1, 1955 he returned home after an evening of drinking and cleaned his shoes with Energine cleaning fluid. Shortly thereafter he experienced generalized body aching accompanied by severe vomiting. The following morning hemorrhages were noted in his eyes. On April 8 his temperature rose to 101° F. and a yellow discoloration of his skin appeared. He was hospitalized April 9, but was ambulatory and did not appear critically ill. On April 12 the urinary volume became scanty and 275 cc. of bloody urine was passed in the following 24 hours. Fluids were then restricted to 1,500 cc. daily and 2 cc. of Mercuhydrin was administered. Dyspnea and orthopnea then appeared, necessitating the administration of oxygen.

Laboratory examinations on April 12 revealed the blood urea nitrogen to be 133 mg. per

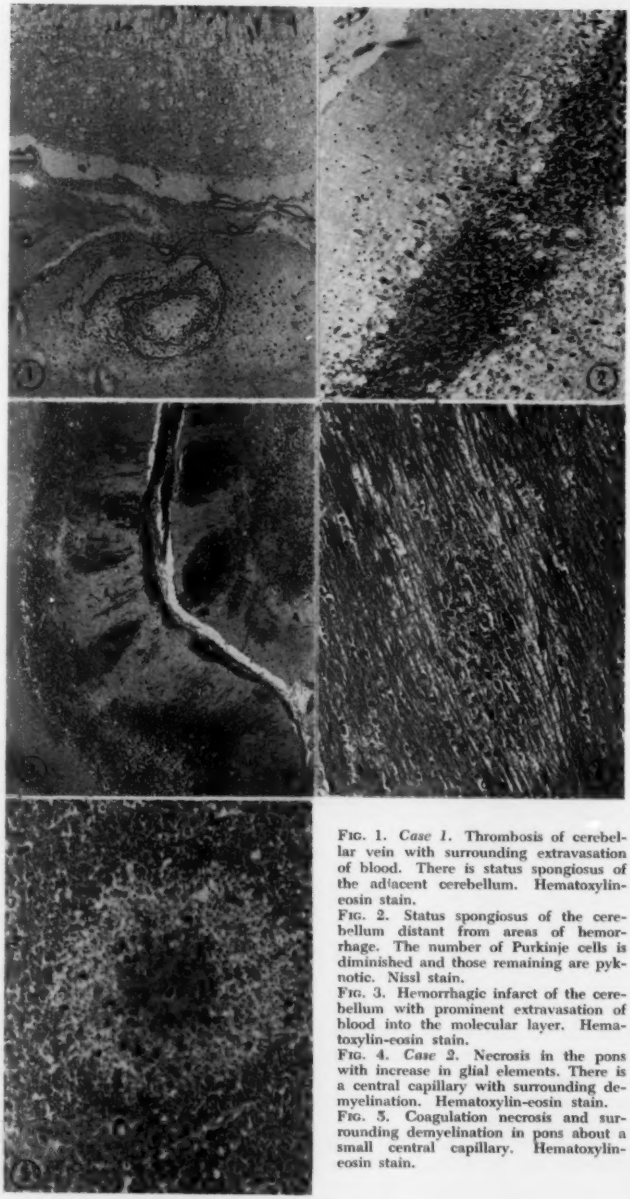

FIG. 1. *Case 1.* Thrombosis of cerebellar vein with surrounding extravasation of blood. There is status spongiosus of the adjacent cerebellum. Hematoxylin-eosin stain.

FIG. 2. Status spongiosus of the cerebellum distant from areas of hemorrhage. The number of Purkinje cells is diminished and those remaining are pyknotic. Nissl stain.

FIG. 3. Hemorrhagic infarct of the cerebellum with prominent extravasation of blood into the molecular layer. Hematoxylin-eosin stain.

FIG. 4. *Case 2.* Necrosis in the pons with increase in glial elements. There is a central capillary with surrounding demyelination. Hematoxylin-eosin stain.

FIG. 5. Coagulation necrosis and surrounding demyelination in pons about a small central capillary. Hematoxylin-eosin stain.

cent, hemoglobin 14 gm. per cent, sedimentation rate 64 mm. per hour, and white blood count 11,750 cells per cu. mm. Urinalysis revealed a trace of albumin and occasional granular casts. An electrocardiogram on April 14 was interpreted as demonstrating a right bundle branch block and exhibited peaked T waves.

The patient was transferred to the University of Minnesota Hospitals on April 15, 1955. At that time physical examination revealed an obese, disoriented, slightly cyanotic white male with Kussmaul type respirations. His pulse was 72, respirations 26 per minute, and temperature 96.8° F. His skin was moist and cool and bilateral episcleral hemorrhages were noted. The skin and sclera were icteric. The inspirations were biphasic, with a prolonged expiratory phase and bilateral inspiratory wheezes in both lung bases. Examination of the heart revealed distant tones and a slightly irregular rhythm. The liver was not palpable and there was one plus pitting edema of the lower extremities.

Laboratory studies. On admission hematologic examination revealed a hemoglobin of 14.3 gm. per cent and white blood count of 14,700 cells, with 93 per cent neutrophils, 3 per cent lymphocytes, and 4 per cent monocytes. The sedimentation rate was 68 mm. per hour and the prothrombin time was 16.2 seconds with a control of 13.1 seconds. The bleeding and clotting times were within normal limits. Urinalysis revealed grossly hemorrhagic urine with a specific gravity of 1.016, 2 plus albumin, and occasional white blood cells in each high powered microscopic field.

Blood chemistry revealed the urea nitrogen to be 186 mg. per cent, carbon dioxide combining power 8 mEq./L., sodium 125 mEq./L., chlorides 90 mEq./L., potassium 8.5 mEq./L., and calcium 8.8 mg. per cent. The total serum bilirubin was 3.9 mg. per cent, with 2.2 mg. per cent after one minute. The serum alkaline phosphatase was 17.9 King-Armstrong units, thymol turbidity test 11 units, and cephalin flocculation 3 plus. The total blood lipids were 39 units. Blood culture was negative and urine culture revealed coagulase negative staphylococcus and diphtheroids. An electrocardiograph revealed peaked T waves, absence of P waves, and a widened QRS complex.

Hospital course. One and one-half hours after admission, 0.8 mg. of lanatocide C was administered intravenously, followed by 500 cc. of 20 per cent glucose solution together with 50 units of regular insulin. The patient became progressively unresponsive and expired seven hours after admission.

Postmortem examination. The principal findings were present in the nervous system, liver, and kidneys.

External examination and section of the brain revealed only congestion of the cerebral vessels. Microscopic examination was performed utilizing hematoxylin and eosin, Nissl, Weil, gallocyanin, Sudan IV, and Mallory phosphotungstic acid stains. The principal alterations appeared in the pons and consisted of small focal areas of demyelination in the transverse pontine fibers and the pontine nuclei. The tegmentum was relatively uninvolved, but occasional areas of demyelination were also present in its ventral portion. Demyelination alone was present in some focal areas, but more commonly a central area of coagulation necrosis was surrounded by demyelinated tissue (figure 4). A small central capillary could be observed in some lesions (figure 5), while in others no vascular relationship could be ascertained. Occasionally a small glial nodule was associated with the areas of necrosis.

The cerebral blood vessels were congested throughout and petechial areas of extravasation of blood were present in the susbtantia nigra as well as in the transverse pontine fibers.

Examination of the liver revealed central necrosis as well as portal fibrosis and regeneration of some hepatic lobule. The kidneys exhibited tubular degeneration.

DISCUSSION

The pathologic findings in these two cases exhibit some features already described, as well as some not previously noted in the literature. The Purkinje cell changes were consistent with those of earlier reports,[2,17] and the areas of pontine necrosis resemble but are not identical with those described by Stevens and Forster.[2] Although cerebellar hemorrhages have been reported,[17] no prior mention of venous thromboses or hemorrhagic infarction of the cerebellum was found in the literature.

The diversity and variability of the

neuropathologic alterations suggested more than a single factor to be in operation in the production of the lesions. Consequently Stevens and Forster[2] suggested as possible mechanisms: 1) direct neurotoxic effect, 2) cerebral hemorrhage, and 3) cerebral fat embolism. The pathologic findings noted in earlier reports, together with those of the present investigations, suggest the responsible factors to be still more numerous and indicate at least the following to be operative in the production of pathology.

1. *Direct toxic action.* The rapid changes in consciousness consequent to carbon tetrachloride inhalation indicate direct action on nervous tissue. When death results from anesthetizing effects the time lapse is often insufficient to allow development of neuropathologic changes. When direct toxic effects do produce neural alterations, the neurons participate in the first visible changes. The Purkinje cell response then appears consistent with such a neurotoxic effect, particularly since these cells are reported to be among the most sensitive to the toxic action of organic solvents.[3]

2. *Augmentation of toxic activity by synergistic compounds.* The synergistic activity of ethyl alcohol with carbon tetrachloride has been adequately documented experimentally and clinically, although the precise mechanism of action remains in doubt. Gastrointestinal administration of alcohol produces an increased absorption of ingested carbon tetrachloride; however, synergism also follows the parenteral administration of these two compounds.[2] The clinical importance of this synergistic activity was well demonstrated by Harris[19] in his report of 78 Navy men employing carbon tetrachloride in cleaning their rifles. Sixty-three per cent of those exhibiting toxic symptoms had ingested alcohol the previous night and 14 of the 15 patients with severe symptomatology had consumed significant amounts. Alcohol ingestion was also prominent in the two cases in the present report.

Other chlorinated hydrocarbons have also exhibited similar examples of synergistic activity with other materials. The anesthetic action of trichlorethylene for mice was said to be potentiated by prior administration of carbon monoxide.[20]

It then appears that such synergistic activity is of potentially great significance, since additional solvents are often utilized with carbon tetrachloride in commercial preparations.

3. *Cerebrovascular involvement.* Three different patterns apparently related to vascular involvement were observed in the two cases in this investigation. The first consisted of areas of pontine necrosis. The absence of phagocytic response two weeks after exposure indicates a recent reaction secondary to vascular effects, rather than the direct effect of the toxin. The other patterns were of venous thrombosis with surrounding hemorrhage and of hemorrhagic infarction. These changes were also accompanied by a minimal phagocytic response 13 days following toxic exposure, again suggesting the parenchymal change to be from recent vascular involvement.

4. *Hepatic or renal damage due to carbon tetrachloride poisoning.* Liver and kidney involvement identical with that regularly produced by this solvent are in themselves capable of producing nervous system alterations.[21–23] In addition, the cerebral hemorrhages previously reported appear to result from diminution of plasma levels of fibrinogen and prothrombin secondary to the hepatic disease.

5. *Pre-existing or concomitant cerebral or extracerebral disease.* Individuals with multiple sclerosis or certain other neurologic disorders have been observed to exhibit lowered tolerance to the anesthetic action of the organic solvents. Pre-existing extracerebral abnormalities such as obesity, diabetes, and hepatic or renal disease have also been reported to diminish tolerance to this poison.[1] Liver damage in particular appears to contribute to the increased susceptibility of chronic alcoholics to carbon tetrachloride poisoning.

Cerebral fat emboli were not found in this investigation or in previous studies. The suggestion of Stevens and Forster[2] of these emboli as a possible mechanism of neural damage in carbon tetrachloride poisoning then remains to be proved.

SUMMARY AND CONCLUSIONS

Two cases of carbon tetrachloride poisoning are presented in which the principal neuropathologic alterations consisted of patchy pontine necrosis and demyelination, Purkinje cell damage, and cerebellar venous thromboses and hemorrhagic infarcts. Review of the literature, together with consideration of these findings, indicates that the variable neural changes in carbon tetrachloride poisoning result from multiple factors. These include: 1) direct neurotoxic effect, 2) synergistic activity with other compounds, 3) cerebrovascular involvement, 4) hepatic or renal damage due to the solvent itself, and 5) pre-existing or concomitant cerebral or extracerebral disease.

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Tissue Changes in the Brains of Cats and Monkeys Following Cobalt 60 Irradiation

George P. Bogumill, Ph.D.

A METHOD has been developed which permits destruction of small areas of the brains of experimental animals with cobalt 60.[1] Since this method has shown great promise in a number of studies, it became important to assess the neuropathology which was produced. In an earlier study[2] in which deep-lying structures were irradiated, a fairly definite sequence of changes was observed to occur, with a stage of acute illness appearing within the first postirradiation week and a second stage of generalized deterioration with a sudden onset and fatal outcome appearing some time after four or more months had elapsed. In addition, the behavioral alterations which occurred subsequent to irradiation with this agent and method varied in regard to time of appearance. Because of these factors, it was considered especially important to establish, if possible, a correlation between changes in the animal's behavior and general condition and changes which might be occurring in the brain at this time. Finally, it is considered that the present study might be useful as an addition to the existing body of information on changes produced in the nervous system by other means of irradiation.

The irradiated tissues subjected to histologic examination in the present investigation were obtained by use of the same materials and methods which were found useful in behavior studies. Monkeys and cats served as subjects. Both species are suitable for use with the stereotaxic instrument, which is used for the application of cobalt 60 radiation to deeper brain areas. In order to obtain information concerning the entire sequence of changes which occur following irradiation, specimens were obtained which covered a range from the immediate postirradiation period up to 256 days.

All the animal subjects received a standard dose of 4,000 roentgens (*r*) calculated at a distance of 5 mm. from the center of the cobalt source (selection of an arbitrary point for measuring the dose is necessary since radiation is dissipated rapidly as the distance from the source increases). Lesions produced by this degree of irradiation had been demonstrated in the earlier studies to produce significant alterations in be-

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havior either when applied to the cortex or to deeper tissues. Though a point source of radiation is merely a theoretical entity, all the calculations for determining the amount of radiation energy delivered to the tissues have been based on the assumption that the center of the cobalt seed did constitute a point source.

EXPERIMENTAL PROCEDURE

The radiation source employed in the present study was a small segment of the radioactive isotope of cobalt secured into the tip of a specially designed 17-gauge needle. A brass plug on the upper end of the needle permitted attachment of the needle to the stereotaxic instrument used to apply radiation to the animal's brain.

For purposes of producing a radiation lesion, the animal was anesthetized with Nembutal and positioned in the stereotaxic instrument. Under aseptic conditions the needle was lowered through a slit in the dura, after the scalp had been incised and a trephine hole made in the bone. The animal was maintained under anesthesia during the four to four and one-half hours needed to provide exposure to the standard dose of this study. At the end of the period of irradiation, the needle was removed, the trephine buttons replaced, and the scalp closed.

Twelve cats and eight Macaca mulatta monkeys of both sexes were used in this study. Five of the cats were irradiated three times, five cats twice, and two cats once each. Three monkeys were irradiated three times each, one monkey twice, and four monkeys once each. The multiple irradiations were performed because preliminary studies had shown the lesion to be small and well localized, thus permitting placement of several lesions in different areas of the cortex in any one animal without altering the picture produced by previous irradiations of a distant area to any detectable extent. In this manner, a total of 27 specimens, each representing an irradiated area, were obtained from the 12 cats and 15 similar specimens from the eight monkeys. Specimens were obtained from each of the species immediately following completion of irradiation and during each of the first four postoperative days. Additional specimens were obtained at time intervals of eight, 16, 32, 64, 96, 128, 160, 192, 224, and 256 days after irradiation. In almost every instance, two lesion specimens were obtained from cats for each of the intervals which have been listed, while the monkeys provided one specimen for each interval.

A control operation was performed for each species by inserting a 17-gauge needle containing no cobalt into the brain for a period similar in duration to that used in actual irradiation procedures. The control cat was sacrificed immediately following operation and the control monkey on the third postoperative day.

After the proper time had elapsed the animals were killed. For this purpose an overdose of Nembutal was administered, and the animals were perfused via the ascending aorta with a 10 per cent formalin-0.9 per cent saline solution, after a preliminary flushing of the vascular system with 50 ml. of warm 0.9 per cent saline. The brains were removed and fixed further in 10 per cent neutral formalin for periods of ten days to three weeks.

All of the monkey brains and four of the cat brains were then embedded in the corn meal-gelatin mixture of Garrett.[3] This produced a firm, easily-cut

block which was sectioned into slices approximately two mm. in thickness. A commercial meat slicer was used to cut sections in the coronal plane. Alternate gross sections through the lesions were stained with a Prussian Blue reaction[4] and photographed (figure 1). Portions of the intervening, unstained slices were used for microscopic examination. For each area containing an irradiation lesion, a corresponding nonirradiated area from the opposite hemisphere was taken as a control. From the eight cat brains which had not been sectioned on the meat slicer, tissue including the lesion was taken from each irradiated area, as well as control tissue from the opposite hemisphere, and subjected to microscopic examination. The tissues were embedded in paraffin, sectioned at eight to ten micra, and the sections were mounted on glass slides with egg albumin. Six stains were used routinely for each specimen and its control: hematoxylin-eosin, thionin, Mallory's collagen stain, Weil's stain for myelin sheaths, Bodian's method for neurofibrils, and a phosphotungstic acid-hematoxylin method for astrocytes and glia fibrils.

RESULTS

In contrast to the animals which had received radiation to deep-lying brain structures in earlier studies, recovery from the anesthetic in the present study was always uneventful. None of the animals in this study exhibited deleterious effects of the irradiation upon their general health and activity at any time. One cat was found dead in its cage two weeks after irradiation, but autopsy revealed the cause of death to be pneumonia. All other animals remained healthy and vigorous until the time of sacrifice.

A general description of the sequence of events will be presented first, and this will be followed by an account of spe-

TABLE 1

SUMMARY OF HISTOLOGIC CHANGES IN CATS AND MONKEYS FOLLOWING COBALT 60 IRRADIATION

Stage	*Cats*	*Monkeys*
Acute stages (0 to 8 days)	Acute necrosis of all neural, glial, and vascular elements along needle track. Hemorrhage, inflammation, edema around this. Gitter cells by third day.	Acute necrosis of all neural, glial, and vascular elements. Hemorrhage not as marked as in cats. Inflammation, edema, and congestion very marked. No glial reaction (reparative).
	Minimum lesion size 1 x 1½ mm. Maximum lesion size 2 x 4½ mm. Average lesion size 1½ x 4 mm.	Minimum lesion size 2 x 2 mm. Maximum lesion size 9 x 7 mm. Average lesion size 6 x 5 mm.
Intermediate stages (16 to 128 days)	Defect filled with gitter cells by 14 days. Blood vessels have thickened walls. Beginning fibrosis of defect. Astrocytosis and beginning gliosis. Secondary necrosis (64 days). Focal, perivascular demyelinization (96 days).	Gitter cells fill defect by 64 days. Fibroblasts with much collagen fill and surround defect. Very slight gliosis at 128 days. Secondary necrosis (64 days). Focal, perivascular demyelinization (96 days).
	Minimum lesion size 1 x 1 mm. Maximum lesion size 2 x 4 mm. Average lesion size 1½ x 3 mm.	Minimum lesion size 3 x 1½ mm. Maximum lesion size 6 x 3 mm. Average lesion size 3½ x 2½ mm.
Late stages (160 to 256 days)	Subpial gliosis (moderate to marked). Slight to moderate fibrosis. Contraction of scar. Perivascular demyelinized areas more confluent. Thick-walled blood vessels in subarachnoid space.	Fibroglial scar which contracts. Thick-walled blood vessels in subarachnoid space. Perivascular demyelinized areas larger and more confluent.
	Minimum lesion size ½ x ½ mm. Maximum lesion size 1 x 3 mm. Average lesion size 1 x 1½ mm.	Minimum lesion size 1½ x 1 mm. Maximum lesion size 5 x 2 mm. Average lesion size 3 x 2 mm.

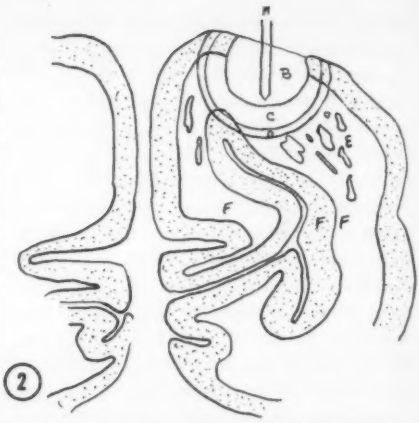

FIG. 1. Photograph of a coronal slice through the brain of a monkey, illustrating the sharp demarcation of the lesion in the cerebral cortex at 16 days.

FIG. 2. A schematic drawing of the lesion in cross section. *A* indicates the position of the needle during irradiation. *B* represents the area of complete dissolution of all cellular elements and smaller blood vessels. *C* depicts the zone of edema which contains petechiae and degenerated cells. This is the area into which the secondary necrosis occurs between 32 and 64 days. A 2 mm. wide zone which contains no astrocytes is indicated by *D*. In the area marked *E* occur the focal regions of perivascular demyelinization. *F* indicates normal cerebral tissue.

cific times of appearance of the changes in the two species. The results are also summarized in table 1 and in a schematic drawing (figure 2).

Use of a standard dose of radiation in cats and monkeys has resulted in tissue changes which are common to both species, although these changes are not of the same magnitude, nor do they follow the same time course. Initially, in both species, there is complete degeneration of all elements – neural, glial, and vascular – for a variable, but sharply demarcated, distance from the radiation source (figure 3). This results in liquefactive necrosis which reaches its maximum extent four to eight days postoperatively. Surrounding this area of acute, complete necrosis, there is a more or less concentric zone of tissue which is markedly edematous and which contains neurons and vessels in various stages of degeneration. Still farther from the center of the irradiated area, isolated pyknotic or swollen, chromatolytic neurons may be seen intermixed with neurons which appear to be entirely normal. Astrocytes are absent or markedly degenerated in this latter region. The damaging effect of radiation upon the blood vessels, both in the region undergoing liquefaction and in the zone of edema, results in the appearance of hemorrhages, of petechial and larger size, during the first few postoperative days.

Microglia soon become transformed into gitter cells, which appear first at the margins of the liquefied zone and later in the perivascular spaces of the regional blood vessels. Fibroblasts also appear relatively early in the postoperative interval. They apparently originate from the blood vessel walls, which are slightly to moderately thickened in areas

containing the heaviest collagen deposits. After a variable period of time, which may be quite long, astrocytes reappear and aid in the formation of a scar by the deposition of glia fibrils. As a result, in the late stages the defect is filled by a compound fibroglial scar.

A secondary necrosis of tissue around the margins of the original defect is present in the 64-day specimens from both species. This secondary necrosis affects all elements in a more or less concentric band around the periphery of the earlier lesion. In addition, the 96-day and longer term specimens from both species exhibit focal areas of demyelinization and axon degeneration which are perivascular in location (figure 4). This degenerative process is progressive and continues to actual necrosis of myelin, axons, and glia, with resultant cavitation. The microglial reaction to these areas is relatively minor.

In spite of the fact that the general course of events is similar in the two species, definite differences in the tissue responses may be pointed out. The major difference is that the size of the lesion in the monkey is several times larger than in the cat; the other apparent dissimilarities may be a result of this feature. In the cat the initial neuronal damage does not extend more than 0.5 to 1 mm. from the site of the needle track, and the vascular damage does not extend more than 0.5 to 1 mm. beyond this. This degree of vascular damage was also found in the control specimen, although the neuronal damage in the control was only what one would expect purely from the mechanical trauma of the needle insertion.

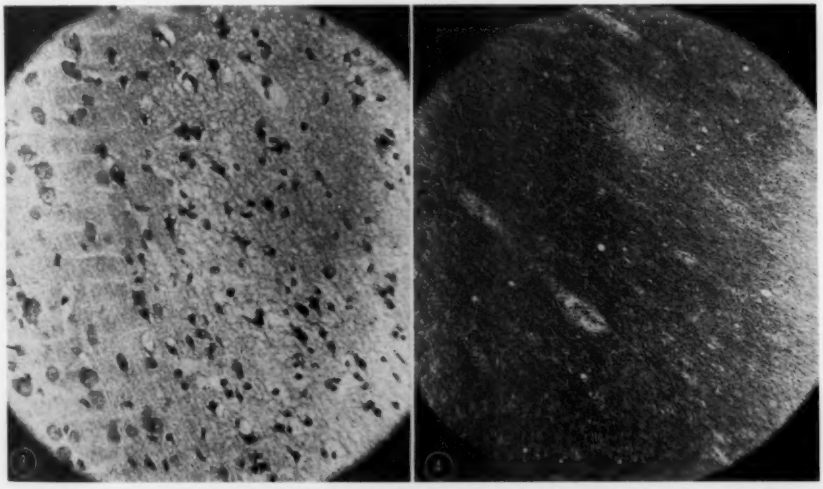

FIG. 3. Photomicrograph illustrating the sharply demarcated edge of the lesion in a monkey. The pyknosis and shrinkage of neurons and glia cells and the slight edema of the tissue in the same region contrast sharply with the normal appearing cortex on the left. Note that the degeneration is quite severe, yet this slide had only very minor petechiae. Thionin stain. x 300.

FIG. 4. Photomicrograph illustrating the location of focal areas of demyelinization primarily around obliterated capillaries. The gitter cell reaction is slight, but many small round cells are seen in these regions. As the lesion progresses, the myelin, axons, and neuroglia become necrotic. 128 days. Weil stain. x 75.

The lesion in the cat increases only slightly in size during the postirradiation interval. In the case of the monkeys, on the other hand, the initial radiation damage to the neurons and neuroglia extends for 2 or more mm. from the needle site. During the first four days the lesion in the monkey increases fourfold in apparent size because of the large amount of edema and inflammation which occur, and it remains larger than the lesion in the cat throughout the remainder of the survival period. Thus, the size of the lesion in the cat remains somewhat constant until scarring develops, while the lesion in the monkey increases markedly in size during the early postirradiation period and then decreases again when edema disappears and scarring begins.

The repair processes begin much earlier in cats than in monkeys. Rod cells (microglia) appear in the cats by the second postirradiation day and begin removing debris, but in the case of the monkeys a similar stage is not reached for more than two weeks. In cats the defect is completely filled with gitter cells by the fourteenth day, but not until the sixty-fourth day in the monkeys. Likewise, astrocytosis and gliosis begin during the first few months in the cats and progress to heavy glial scarring, but gliosis is minimal in the monkey as late as 128 days and is not marked in any of the specimens studied.

The appearance of fibroblasts and the deposition of collagen occur at approximately the same time in both species, but the degree of fibrosis progresses much further in the monkeys and results in complete encapsulation of the defect by the ninety-sixth day, while in cats the fibrosis does not become extensive at any time. Thus both species repair the defect with a compound fibroglial scar; in the cat gliosis is more pronounced, whereas fibrosis is slightly more important in the monkey.

DISCUSSION

One aspect of the results of this study which was not anticipated was the marked difference in reaction of these two species. The existence of a pronounced species difference is important to recognize in and of itself, since it serves to emphasize the importance of exercising caution in drawing conclusions about irradiation from animal studies alone. Beyond this, it would be most desirable to discover reasons for the existence of the species differences. One hypothesis emerges from this study when it is considered in conjunction with information about the relation between oxygenation of tissues being irradiated and the severity of the resultant effect. The cats in the present study required less Nembutal for each irradiation period than did the monkeys (average difference of 18.4 mg. per kilogram of body weight), and yet remained at lower levels of anesthesia throughout the irradiation period. Furthermore, monkeys recovered from anesthesia much more readily, showing little persistent effect on the day following, whereas the majority of the cats remained groggy and depressed for 24 to 48 hours after completion of the irradiation period. Study of the lesion specimens obtained immediately following irradiation in both species showed a partial to complete closure of many of the vessels in the immediate vicinity of the needle in the cats, while the same area in the monkey specimens exhibited a marked congestion.

Since oxygen is necessary during irradiation to produce an effect on biologic

systems,[5] and since oxygen consumption by the brain decreases progressively in deeper stages of anesthesia.[6] the two factors combined may have had a role in protecting the cerebral cortex of the cats more than was true in the monkeys.

The present study shows clearly that the cortex of the cat is more radioresistant than that of the monkey. Such a finding appears to indicate that a dose of radiation to which the brain of a lower form such as a cat or rat is resistant may well cause extensive damage to the central nervous system of a monkey or man. Thus transferring dosages derived from animal experiments to irradiation of human tumors may be very hazardous.

The difference in the effect of irradiation in the two species may have a bearing on the problem of relative sensitivity of the vascular and neural elements of the brain. Many investigators,[7–13] using a variety of species and a variety of methods, have concluded that the vascular elements are sensitive and the neural elements resistant to irradiation. Other investigators[14–19] have taken an opposite view. In the present study no definite conclusions can be drawn supporting either view, although isolated damaged neurons were often seen 2 or more mm. further removed from the needle than the maximum extent of the initial edema and vascular degeneration. These neurons were far enough from the needle to have received doses in the range of 1,000 or less roentgens, and exhibited pyknosis of the nuclei with swelling of the cytoplasm Such changes were not seen in the specimens of control cortex removed from the opposite hemispheres of the same animals. The presence of such damaged neurons might indicate that the neural elements are more sensitive than the vascular.

On the other hand, the delayed necrosis seen in the present study may be due to a delayed breakdown or thrombosis of the blood vessels. The demyelinization which appeared after three or more months had elapsed following irradiation was perivascular in location and was progressive. It is difficult to determine whether this was due to a progressive change initiated in the blood vessels, as suggested by Pennybacker and Russell,[13] or whether the vascular degeneration in these regions was secondary to myelin degeneration, as suggested by Arnold and co-workers.[19] Possibly the delayed demyelinization may have some relation to the finding by Reynolds[20] that myelin may be altered optically and functionally by the irradiation without changing its outward physical form for long periods. Another possibility is that blood vessels in and on the edges of the early lesion were damaged but not immediately destroyed. This damage might result in impaired blood supply to deeper branches of these vessels, with slowly progressive destruction of the areas supplied by such branches. More study is necessary before the question of relative sensitivity will be settled conclusively.

SUMMARY

1. Areas of the cerebral cortices of cats and monkeys were irradiated, utilizing a small segment of cobalt 60 fastened into the tip of a 17-gauge needle. A standard dose was employed and was identical in the two species. The animals were killed at varying intervals from zero to 256 days, and the lesions were studied microscopically.

2. The radiation produced complete liquefaction of all elements (neural,

glial, and vascular) for a short distance immediately around the radiation source. Vascular degeneration resulted in hemorrhage and edema. Gitter cells removed the debris, and fibroblasts and astrocytes combined to produce a fibroglial scar. Secondary necrosis was found at 64 days around the original defect, and focal perivascular areas of demyelinization appeared at 96 days in the white matter.

3. The size of the lesion in the monkeys was substantially larger than in the cats. This species difference was interpreted as possibly having been associated with a more severe hypoxia in the cat cortex during irradiation, which in turn may have been the result of response to the anesthetic.

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Anticoagulation Therapy in Cerebral Thrombosis and Embolism

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A CEREBRAL VASCULAR ACCIDENT immediately raises the question of the nature of the underlying pathologic process – hemorrhage, thrombosis, embolism, ischemia due to low blood pressure or cardiac insufficiency, or vascular spasm. The etiology is not always determined by exact tests at our disposal; therefore, the diagnosis is usually a clinical one. Recurrent and reversible cerebral palsies have been ascribed to cerebral vascular spasm,[1] notwithstanding evidence that cerebral vessels showed feeble vasomotor function in comparison with peripheral vessels. Based on the spastic theory, treatment by vasodilator drugs, stellate blocks, and cervical sympathectomy has recently been much in vogue. Neither in theory nor in practice has this approach been entirely satisfactory.[2]

Millikan and his associates[3,4] have advocated the use of anticoagulants to prevent recurrence in patients who have repeatedly shown impairment of circulation by occlusion within the distribution of both the internal carotid and basilar arteries. This paper concerns anticoagulant treatment of this type of cerebral vascular accident as well as initial attacks. Our material consists of 26 cases studied between July 30, 1954 and January 15, 1956, and 39 controls. Cases of thrombosis secondary to embolism have been included.

Since the discovery of Dicumarol in 1941 by Link and his associates,[5,6] there has been much work done in the field of anticoagulant therapy in postoperative and coronary thrombosis cases.[7–10] As yet, cardiologists have not adopted this treatment as routine therapy.[11] Studies of this nature for cerebral infarction are still incomplete. Among others,[12,13] Wright and McDevitt[14] have made important contributions to anticoagulant treatment.

SELECTION OF CASES

In this study, consecutive admissions with cerebral vascular accidents were examined with special reference to prior and reversible attacks, state of the blood pressure and of heart function, and manner of onset. A lumbar puncture was performed routinely in order to determine the presence or absence of red blood cells in the cerebrospinal fluid. In consecutive admissions for cerebral vascular accidents, hemorrhages occurred about once in every ten cases. In the absence

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of red blood cells, it was assumed that the etiology was probably cerebral anoxia or infarction by thrombosis or embolism. Cases were excluded in which red blood cells were found in the cerebrospinal fluid. Patients seen within 48 hours of the onset were placed on the study program and anticoagulant treatment begun. Reversal of the pathology already present in the infarcted brain was not anticipated, but it was hoped that further progress of the infarction or thromboembolic complications might be prevented. Moreover, analysis of some of the case reports in the literature almost leads one to the conclusion that some specific ameliorative effect upon the cerebral circulation or tissues can be attributed to the anticoagulant drugs over and beyond their acknowledged effect on clot formation.

METHODOLOGY

Whenever possible, an initial prothrombin time* level was established,[15] followed by the administration of heparin 50 mg. parenterally at four-hour intervals for a total dose of 200 to 300 mg., and Dicumarol 200 to 300 mg., initially by the oral route with subsequent doses regulated by daily prothrombin time levels. An effort was made to maintain the prothrombin time level at approximately twice the control time, or between 10 to 20 per cent.** Where complications of bleeding such as ecchymosis or hematoma occurred, Dicumarol was stopped. If the complications progressed, the case was treated with vitamin K and/or transfusion to raise the prothrombin time level to within normal limits. Progress of the neurologic deficit was checked by daily bedside clinical evaluation. In similar fashion to the control cases, treatment cases were observed for initial periods of bedrest, followed by graduated courses of physical medicine.

RESULTS

Over an 18-month period, 26 treatment cases were studied in 24 patients. Their ages ranged from 33 to 83 years (average 64). Sixteen of the group (61 per cent) had a history of well-established hypertension and/or cardiovascular disease, while 12 (46 per cent) gave a history of at least one previous cerebral infarction. Six of the 26 (23 per cent) died during the observation period (two within an interval of four days from admission), 14 (54 per cent) left the hospital walking, and six (23 per cent) had achieved wheelchair status at discharge.

Autopsies obtained in four of the six deaths revealed the following: 1) thrombi in aorta and right iliac artery as well as basilar artery, 2) thrombi in right femoral vein and pulmonary arteries as well as left internal carotid artery, 3) thrombi in right pulmonary artery as well as right middle cerebral artery, and 4) bilateral bronchopneumonia as well as a thrombus in left middle cerebral artery.

As indicated in table 1, the control group of 39 cases was comparable to the treatment group in its selection, as shown by the similar age range and incidence of hypertension and prior history of cerebral pathology. The deaths and degree of recovery of the survivors also followed closely the percentages that occurred in the treatment group. Of the six deaths, autopsies in two re-

*In this laboratory, Simplastin, a commercial thromboplastin extract, was used in determining the prothrombin time. The time in seconds was compared to a control on a curve and expressed in percentage of normal.

**11 to 23 per cent recommended by the First Anticoagulant Committee of the American Heart Association (Am. Heart J. 36:801, 1948).

TABLE 1
COMPARISON BETWEEN THE STUDY AND CONTROL GROUPS

	Study	*Control*
Number of cases	26	39
Age range	33-83 (av. 64)	43-83 (av. 64½)
Previous strokes	12 (46%)	17 (44%)
Previous cardiovascular disorders	16 (61%)	25 (64%)
Deaths	6 (23%)	6 (16%)
Discharge status		
Ambulant	14 (54%)	25 (64%)
Wheelchair	6 (23%)	8 (21%)

vealed: 1) thrombosis of left middle cerebral artery, and 2) petechial hemorrhages and platelet thrombi in the brain.

The duration of hospitalization of the treatment series and of the controls was approximately the same.

Complications encountered during anticoagulant administration were recurrence of signs and symptoms (extension of thrombus) in two cases and ecchymosis and/or hematoma in two cases. All four complications occurred while the prothrombin time level was within the therapeutic range of 10 to 20 per cent. In one case anticoagulant therapy was continued on an outpatient basis following hospitalization. This therapy was discontinued after several weeks because of the variabilities found in the prothrombin time level (taken every two or three days) and the inability to maintain a satisfactory prothrombin time level.

Two cases are presented to illustrate progression of thrombosis during anticoagulant administration.

Case 1. A 57 year old white veteran was admitted to the hospital on March 29, 1955, a few hours after awakening with weakness of the right upper extremity, headache, and difficulty in speech and swallowing. Spinal fluid on admission was under normal pressure and showed no increase of cells or protein. The neurologic examination showed slight weakness of the right upper extremity, with the grip measuring 20 kilograms on the dynamometer compared to 70 for the left. There was slight hesitancy of speech and the tongue deviated to the right. He was placed on heparin followed by Dicumarol, and a prompt elevation of prothrombin time was obtained, ranging between 25 to 40 per cent of normal. By April 6 he had improved markedly. His grip now measured 90 kilograms bilaterally, there was no difficulty in speech, and the tongue was in the midline. He was discharged from the hospital, only to return three days later with recurrence of dysarthria, weakness of the right hand grip, and slight numbness of the right upper extremity. His prothrombin time had returned to 100 per cent. Dicumarol therapy was resumed and the blood prothrombin time was maintained in the range of 25 to 40 per cent of normal. On April 25, while still receiving Dicumarol, he was suddenly stricken with severe right hemiplegia. Suspecting a hemorrhage, the spinal fluid was again examined at this time, but it was clear and colorless and contained no cells. The left carotid pulsations were not obtained and neurosurgical consultation was ordered. Upon opening the left common carotid artery, a loosely attached sclerotic plaque was found at the bifurcation between its internal and external branches and removed. The plaque was semicircular, constituting a partial cast of the carotid artery, and had a freshly formed clot attached to it. Postoperatively there was temporary slight improvement in the patient's mental confusion, but he remained severely hemiplegic on the right and completely aphasic. No further Dicumarol was given after surgery and the prothrombin times returned to approximately 100 per cent. He expired May 6, seven days postoperatively. Autopsy showed a massive infarct of the left cerebral hemisphere, a thrombus in the left internal carotid artery, another thrombus in the right femoral vein, and emboli in the pulmonary arteries.

Summary. A patient with recurrent episodes of neurologic symptoms referable to embarrassment of the internal carotid artery supply eventually developed complete occlusion of this vessel while receiving anticoagulants and with his prothrombin time in the range of 20 to 40 per cent.

Case 2. A 65 year old white veteran was admitted to the hospital on September 12, 1955. He had had right hemiplegia eight to ten years previously and a second stroke five

years later, involving speech and swallowing with some recovery on each occasion. One week prior to entry he had developed weakness of the left side of his body for the first time, with gradual progression of disability so that he was unable to talk or speak on the day before admission. Examination on admission showed left facial paralysis, complete aphonia, and dysphagia. Blood pressure was 120/75. There appeared to be nearly normal strength in the extremities and no Hoffmann or Babinski signs were obtained. The clinical findings were suggestive of basilar artery occlusion. He was placed on anticoagulant therapy on September 14 and, after some initial fluctuations, a level of approximately 20 to 30 per cent of normal prothrombin time was obtained. The patient recovered some ability to swallow. However, on the twelfth day of treatment, while the prothrombin time was approximately 20 per cent of normal, he had evidence of extension of brainstem damage with complete dysphagia and died of respiratory failure in 48 hours. At autopsy he had a "pipe-stem" basilar artery with occlusion by antemortem thrombus, as well as old softenings in the right frontal and parietal and left occipital lobes, mural thrombi in the aorta, and a fresh thrombus in the right iliac artery.

Summary. A patient with recurrent episodes of bilateral cerebrovascular embarrassment over a period of about ten years eventually developed partial and later complete occlusion of the basilar artery while on anticoagulants with his prothrombin time in the range of 20 to 30 per cent of normal.

INHERENT DANGERS IN THE METHOD

Hemorrhage is the first and most obvious danger that may be mentioned in connection with anticoagulant administration. Figures 1, 2, and 3 illustrate the marked variation in individual sensitivity and response to these drugs. The degree of bleeding one may encounter ranges from microscopic petechiae to massive hematoma. To some extent the physician can prevent the more serious degrees of hemorrhage by early recognition of the danger and prompt counterattack with vitamin K and transfusion.

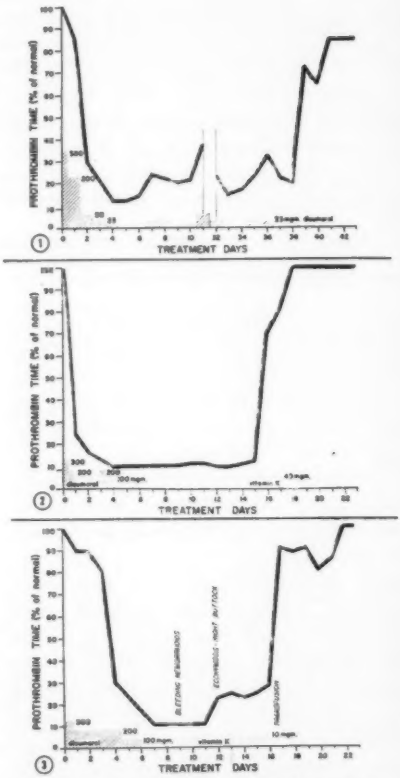

FIG. 1. A case illustrating the usual response to Dicumarol administration, reaching the therapeutic level in three to four days, and return to normal range two or three days after the drug is discontinued. Note: Broken line indicates period of omitted prothrombin time determination.

FIG. 2. A case illustrating a rapid response to Dicumarol administration, reaching the therapeutic level in one to two days. Vitamin K was given to effect return of the prothrombin level to normal limits following a prolonged depression of the level after Dicumarol was discontinued.

FIG. 3. A case illustrating a delayed response to Dicumarol administration, reaching the therapeutic level in five to six days. Due to complications of bleeding, vitamin K and finally a transfusion were necessary to achieve return of the prothrombin level to normal limits.

We believe there is a greater chance that dangerous levels of prothrombin time

may go undetected if patients are managed on an outpatient basis, particularly without frequent prothrombin time determinations. For example, in the patient whose data are charted in figure 2, the prothrombin time remained at 10 per cent of normal for ten days after the last of four doses of Dicumarol and showed no tendency to rise to safer levels until vitamin K was administered. One can imagine the possible complications if such a patient on an outpatient status were placed on a predetermined dosage schedule without daily prothrombin time determinations. Such complications have been reported in previous anticoagulant therapy studies. Nichol and his associates[16] found the incidence of hemorrhagic complications to be 25 per cent. These consisted of hematuria, hematoma, melena, rectal bleeding, epistaxis, hematemesis, hemoptysis, and one retinal hemorrhage in a diabetic. Cloward and Yuhl[17] reported a case of paraplegia due to intraspinal hemorrhage. Most internists have felt that the inherent risks involved do not offset the probable advantages received by this treatment. However, in the present series the advantages to be derived from anticoagulant therapy in reducing the complications or extension of cerebral infarction do not seem to be clearly proved. On the other hand, the possibility that the dangers of bleeding may be increased if the method attains wide use in office practice of ambulatory neurologic patients requires at least an admonition of caution.

CONCLUSIONS

In comparing this small series of 26 cases on anticoagulant therapy with 39 control cases, there was no appreciable difference in the mortality rate, the incidence of complications, or the natural course of recovery between the two groups.

Presence of recent antemortem thrombi in two of four cases in the treatment group at autopsy is reported, and this finding suggests that prolongation of prothrombin time is not in itself sufficient to prevent intravascular blood clotting.

For the same reason, the efficacy of anticoagulant treatment where the prothrombin time level is below 50 per cent but above the therapeutic level of 10 to 20 per cent is doubtful, in spite of its reported success by others[18] in the ambulatory cases.

Careful hospital control of anticoagulant treatment with Dicumarol is necessary because of the narrow margin between the therapeutic level and the hemorrhage level, as well as the difficulty in maintaining the therapeutic level without daily prothrombin time level determinations.

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■ The signs in apoplexy which have been generally considered as favourable, are, a moderate degree of the disease; a warm, gentle, general perspiration; excretions of blood from various parts of the body, particularly from the nose, or from the haemorrhoidal vessels; and a free state of the bowels. Hippocrates says, that the accession of piles is useful to apoplectic persons. Schacht observes, that the accession of piles, the menses, ptyalism, and copious warm perspiration, is favourable in apoplexy. Dolaeus says, that apoplexy is often cured by salivation, and describes the case of an apoplectic woman who was thus relieved, but who died on the ceasing of the salivation. Goavarts, in his Dis. Med., remarks, that nature sometimes spontaneously relieves apoplexy by large haemorrhage from the nose, by ptyalism, by warm and copious perspiration, and a free flow of the urinary or alvine evacuation.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Epilepsy and Life Insurance

Alex J. Arieff, M.D.

INTEREST IN THIS EQUIVOCAL SUBJECT came about as a result of two experiences. The first was as a clinician acting as a go-between for the epileptic patient and the insurance company. Secondly, while serving on the committee for epilepsy legislation, it has become clear that a problem exists which can only be solved eventually by a lot of research and collaboration by actuarial societies, insurance companies, neurologists, societies dealing with epilepsy, public health agencies, and the like.

The purpose of this study is to determine the current status of insurance with respect to patients with an epileptic or convulsive disorder. From this data and what is currently known about epilepsy, it should then be possible to obtain a reasonable and fair insurance status for persons suffering from various types of convulsive disorders. It is important to recognize that epilepsy is not a disease but a protean symptom which may consist of alterations of consciousness alone, or convulsions of various degrees, or episodic behavior disorder.

A simple classification may be followed, such as the one currently used at Northwestern University Medical School clinics:

1. Symptomatic or organic, causing
   a) focal spells
   b) momentary alterations in consciousness
   c) generalized convulsions.
2. Idiopathic where cause is not evident.
3. Associated with mental deficiency.
4. Types of seizures:
   a) petit mal
   b) grand mal
   c) psychomotor (equivalents)
      1) focal seizures
      2) akinetic.

In order to evaluate people with convulsive disorders, it will be necessary to have as much medical information as possible about the person with this disorder and then follow him until he dies. Then it would be necessary to evaluate the relationship between epilepsy and cause of death. This would give us sensible life table studies of a large population of epileptic patients classified in various ways to obtain survival rates for comparison with survival rates of the corresponding "normal" population. Epidemiologic studies in a community are

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Read at the eighth annual meeting of the American Academy of Neurology, St. Louis, Missouri, April 28, 1956.

valuable. Follow-up studies, such as Walker's on posttraumatic epilepsy,[1] are of utmost value.

The project was started by sending a letter to most of the medical directors of Life Insurance Companies (92 in the U. S. and Canada). The response from them was most favorable and helpful.

The literature on this subject was also investigated and found informative, but not adequate, especially with respect to incidence, follow-up studies, and mortality studies. Lew[2] of the Metropolitan Life Insurance Company has shown how physical impairment studies by individual insurance companies and actuarial societies have increased our clinical knowledge specifically on refined prognosis.

Boland[3] and Yochem[4] in their evaluation of special risks emphasize the difference existing between clinical medicine and insurance medicine. While the clinician evaluates a patient as an individual, the life insurance physician appraises the individual only in a group based on life insurance statistics. While the patient is usually anxious to outline all his symptoms in detail to his personal physician, his attitude is quite the contrary with an insurance examiner. The clinician stresses the individual short-range future, while the life insurance underwriter stresses the long-range viewpoint. The clinician can be optimistic and reassuring to an individual with a mild impairment, while in life insurance underwriting, impairments are grouped according to life expectancy of the group.

Although epilepsy or the convulsive state is a fairly common illness, accurate statistics are wanting. The incidence varies from 0.5 to 1.5 per cent of the population and there may be one-half or one and one-half million people suffering from convulsive states. The Metropolitan Life Insurance Bulletin of August 1951 estimates that there are 500,000 to 800,000 people with epilepsy in the United States.[5]

Kurland and Berkson[6] have made an ideal epidemiologic survey of the incidence of epilepsy in a small urban community from 1945 to 1955 (ten years). They divided the convulsive disorders into: 1) generalized convulsions with fever, 2) other generalized convulsions — grand mal, 3) petit mal, 4) focal cerebral seizures, and 5) miscellaneous. Under each of these there were subdivisions according to etiology: 1) primary and 2) secondary. Under "febrile" there were 101 infants and children. Under grand mal primary there were 66 children and adults. Four of these died (age 31, suicide; age 59, exfoliative dermatitis due to anticonvulsant medication; age 40, carcinoma; age 10 months, convulsion with cerebral edema and extradural hemorrhage). There were 23 subjects with "constitutional" grand mal (one patient died of suicide, age 31). There were 14 patients with petit mal. Of cases of grand mal secondary to supposed known etiology, there were 11 due to congenital defects, six due to trauma, 14 due to infections, five due to alcoholism (one woman died of subdural hemorrhage), three due to S.M.A. formula, four due to brain tumor (underreported), and 12 were due to vascular disorders. In the focal group there were 23 cases. There were 21 cases of focal motor, two cases of focal sensory, and two cases of focal sensorimotor seizures. Under miscellaneous seizures there were six cases. The city of Rochester, Minnesota was the community and the population was 29,885 as of April 1950.

Walker[1] made a 10-year follow-up study of 246 head-injured men who had at least one epileptic episode. Approximately one-half were personally examined at least four years after injury and the rest followed by questionnaire; 81 per cent were followed over ten years and 98 per cent more than five years. Of the original 246 men, 17 are dead, the majority as a result of their wound. This is about five times normal expectancy. Two were killed in auto accidents, two died as a result of a convulsion, one committed suicide, and two died of causes unrelated to the nervous system. Of the entire group, 34.4 per cent are employed full-time and 11.1 per cent part-time; 63.2 per cent had no major attacks for more than two years and 57.6 per cent had had no attacks five to ten years after injury. This is important insurance-wise as well as medicolegally.

Young,[7] discussing underwriting consideration in epilepsy, gave a comprehensive review of the subject in 1954 and emphasized the paucity of the literature. Epilepsy is a minor cause of death in the United States, with a rate of 1.3 per 100,000 population (1948 statistics of the Metropolitan Life Insurance Company). The Medical Impairment Study of 1929 gave mortality as two and one-half times the standard risk. The Medical Impairment Study of 1951 gives approximately 208 per cent mortality in petit mal and 318 per cent in grand mal epilepsy, which is very little different from the study in 1929. However, in the actuarial studies of 1951, there were only 377 entrants of grand mal epilepsy with one or more attacks, the last over five years prior to the application. There were 11 deaths involving 21 policies. The expected deaths were 5.40, which gives a mortality ratio of 389 per cent or 21 policies per 5.4 expected deaths. In this same study with respect to cause of death, there were two deaths due to accidents and homicides involving nine policies, which gave a mortality ratio of 1,059 on the substandard group. Other examples by cause of death in this study for standard and substandard were nine policies on five lives due to accident and seven policies on one life by homicide where 2.75 were expected for both causes. Three policies on two lives terminated by suicide where 0.69 was expected; four policies on two lives terminated by epilepsy where 0.01 was expected; 11 policies on ten lives terminated by death from heart and circulatory system (5.53 expected); six policies on six lives terminated by central nervous system vascular disease where only 0.53 was expected. These are the bases by which mortality tables and ratings are determined. It can be seen the number of cases are too low to give an accurate rating, but these are the only available figures. These studies were gathered from 27 life insurance companies in the United States and Canada covering the period from 1935 to 1950.

Schwade's reference[8] to more accurate figures concerning epilepsy as a cause of death is pertinent. In the state of Wisconsin, there were 70 deaths reported from epilepsy in 1953, or 0.2 per cent of the total deaths, which gave a rate of 2.0 per 100,000 population. The crude death rate for all causes was 9.8 per 1,000 population. Of the 70 deaths, it was found that 14 were due to status epilepticus and 12 were from accidental consequence of the seizure. These 26 were only 32.5 per cent of the 70 deaths which were really due to epilepsy itself. Similar studies over the country would

certainly be helpful in showing that epilepsy is a rare cause of death.

In the Illinois Department of Public Welfare statistical research section,[9] there were 378 deaths reported in epileptic patients between 1951 and 1955. Where cause was known the majority of patients died of cardiovascular disease or pneumonia. None were known suicides or died from the result of a convulsion alone. In 250, or 13 per cent, the death was due to disease of the central nervous system or cerebrovascular disease. The median age of death was 45 to 49 years. These statistics are all from chronic institutional patients.

In the Craig Colony which is intended solely for treating epileptics who are not mentally ill or defective, the average age at death is 44.8 years. The idiopathic group had a higher average at death than the symptomatic group. Of 63 deaths in 1951 and 1952, 27 or 42.9 per cent were considered due to epilepsy.

Steinsick,[10] in 500 autopsy studies from 1933 to 1948, found the average age of death in idiopathic epilepsy was 39.6 years and in symptomatic epilepsy as 31.3 years. These, however, are institutional statistics and are not valid for extramural or outpatients.

Lennox,[11] from census data, assuming that one in 200 people is epileptic, figured the death rate from epilepsy in 1905 was 18.3 per 200,000 population and fell in 1948 to 2.6. Other studies show that the rate is high in early life for epileptics and low after the age of 50 years.

Prudhomme[12] in 1941 found 57 suicides among 62,000 institutionalized epileptic patients. At the Craig Colony, the suicide rate was 45.6 per 100,000 epileptics or about five times that found in the general population, which is about 9.7. Of a 15,000 extramural group, there were only ten known suicides.

In a 12-year résumé, 1935 to 1948, Arieff[13] (in the Clinic for Convulsive Disorders, Northwestern University Medical School) found 17 known deaths among 543 patients of which two were due to suicide, one was due to status epilepticus, and three died of brain tumor. Twelve of the 17 patients died under 50 years of age. It is noteworthy that only two of the 17 patients who died were controlled of seizures by medication.

On the brighter side, Yochem[4] has shown in his evaluation of special risks that former uninsurable individuals are now able to be insured. During 1950 there were 600,000 extra-risk policies purchased amounting to $1,800 million, increasing the total number of these policies to four and one-half million amounting to $9,600 million.

Yochem's points on evaluation of insurability in epilepsy depend on: 1) severity of disease, 2) frequency of attacks, 3)duration of illness, 4) type of epilepsy, 5) age of applicant, 6) occupation, and 7) time elapsed since last attack. Rating for epilepsy decreases as the length of time since last attack increases. However, rating may be required even ten years after last attack or even more, depending on the above factors.

Denker[14] in 1948 elaborated on some of the problems of insurability of epileptics, pointing out that "If an intelligent and cooperative individual while under observation and treatment has had his attack either completely eliminated or reduced to one or two yearly, if he has been able to carry on adequately in his business or professional

endeavor, and if his habits as to alcohol are abstension, I believe he can be safely insured at some slight to moderate substandard rating." With time and observation, such a rating can be gradually reduced as his favorable course is maintained over a large number of years.

Dingman, in two studies on risk appraisal[5] and selection of risks,[16] made some statements which do not coincide with present-day observations: "Because of self-consciousness, epileptics have marked personality changes. They incline to be introspective, emotionally unstable." . . . . "Individuals below par in their mental health are almost invariably emotionally unstable." . . . . "He takes to drink easily. His ailments tend to get worse rather than better." . . . . "Not occasionally a general mental *deterioration* sets in."

These statements are not borne out by clinicians treating extramural patients with epilepsy. Stone and Arieff[17] found the personality disorders in epilepsy coincided with the general population. Yacorzynski and Arieff[18,19] found that less than 5.0 per cent of epileptics deteriorated and these were due to the brain disease rather than convulsive symptoms.

Dingman offered a prognostic index based on age at onset: Childhood – unsatisfactory, 15 to 20 – 50 per cent chance of arrest, 25 to 35 – outlook obstinate, 35 and over – outlook brighter. He, however, emphasized that freedom from attacks for years makes the patient less of a risk and, if that period is over five years, the rate may be average.

Dingman stated that "disability and accidental death policies are never permissible." However, Johnson, in discussing Young's comprehensive paper,[7] attempted to apply the statistics on his evaluation of risk. He classified patients uninsurable as follows: 1) all between six and 26 where seizure has occurred within one year, 2) all between 25 and 65 whose first seizure has occurred within two years, 3) all between 15 and 29 without average school or work record and with any unfavorable alcohol, driving, or marital history, 4) all with more than one episode of status epilepticus, and 5) all with psychomotor epilepsy, the behavior and expression of which is subject to cultural misinterpretation.

From this brief survey of the literature, including some personal experience, one can recognize that there is a problem which obviously needs more study, especially if the patient with epilepsy is to be given a fair evaluation. The only fair solution is a collaborative project whereby true actuarial studies could be obtained. This would entail cooperation of neuolrogic clinicians and others interested in epilepsy, including special clinics. These clinicians and clinics working together with insurance companies could finally obtain accurate statistics on the risk involved when patients with epilepsy apply for life insurance. This could be accomplished first of all by standardizing the classification for type and etiology of epilepsy in all clinics, then keeping an accurate follow-up of these patients until time of death. With the aid and methodology of insurance companies, accurate actuarial studies would then be available for a final fair evaluation of insurability.

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■ Although I have spoken of epilepsy, there are really very many epilepsies, and thus, illustrating by the eye symptoms (vertigo, colour, alterations in size or distance of objects), we should try to find the particular sequence of symptoms of other kinds, of which each of the eye symptoms is the prelude. Epilepsy is not a complex thing when it is empirically regarded as a clinical entity, which for some purposes it should be. It is comparatively easy to note the "causes," "warnings," etc., "of epilepsy;" much good work has been done in that way. But, besides investigating in this way, we have to "turn ourselves round" and try to ascertain what different symptoms result from differently seated "discharging lesions" of the highest centres. We have the large compound question to answer, What is the constitution of the "organ of mind" (highest centres) by which it results (1) that discharges beginning in different parts of it produce different epilepsies – produce, if severe enough, nearly universal effects (no doubt, in different degrees and sequences); whilst (2) other kinds of disease of different parts of the "organ of mind" produce different insanities? (3) In one case we may have, first, in the paroxysm, cessation of consciousness with universal convulsion and equivalent effects in the organic field, and then, after the paroxysm, insanity – acute temporary dementia (coma) or "loss" of consciousness, with mania. After epileptic fits of different degrees of severity we have different degrees of insanity, from "confusion of thought" to coma. Indeed, some physicians go so far as to say that an attack of mania sometimes occurs instead of an epileptic convulsion; as I have implicitly said, when speaking of movements properly so called and of elaborate mental states, I do not hold this hypothesis. (4) We have to find a basis for the comparative study of epilepsies and insanities (diseases of highest centres) with diseases of lower centres.

J. Hughlings Jackson in *Ophthalmology and Diseases of the Nervous System,* published in 1886.

Subarachnoid Hemorrhage in Subacute Bacterial Endocarditis

Homer Ray, M.D. and Krishna M. Wahal, M.D., Ph.D.

SUBARACHNOID HEMORRHAGE is a relatively infrequent complication of subacute bacterial endocarditis. We wish to present four cases in which subacute bacterial endocarditis was complicated by bleeding from a cerebral aneurysm. In cases 1 and 2 the hemorrhage was due to the rupture of a mycotic aneurysm, in case 3 to rupture of a "congenital" saccular aneurysm following septic embolism of its fundus, while in case 4 bleeding followed inflammatory necrosis of the wall of a congenital aneurysm and one of the stem arteries originating from its sac.

Case 1. An 11 year old white male child with congenital heart disease was admitted with joint pains and fever. Blood culture showed gram-positive cocci. Two days before death, the child complained of headache, vomited, and became unconscious. At this time bilateral Babinski signs were present and the pupils were dilated.

At necropsy, subacute bacterial endocarditis of the aortic valve was associated with coarctation of the aorta and an interventricular septal defect. Subarachnoid hemorrhage was present over the entire right hemisphere. The source of bleeding was a mycotic aneurysm of one of the subarachnoid arteries. This vessel was partially occluded by infected material which had produced a focal area of arteritis and necrosis. As a result, there had been extravasation of red blood cells and neutrophils into the subarachnoid space, as well as areas of purulent encephalitis and infarction in the adjacent cerebral tissue.

Case 2. A 55 year old colored man was admitted with decompensated rheumatic heart disease. During his hospital stay, he showed a remittent type of fever and was confused and disoriented. Blood cultures were positive for gamma enterococcus on several occasions. One week before death, he developed extraocular palsy on the left and right hemiparesis. Spinal fluid at this time was clear and contained 26 white blood cells.

Necropsy revealed subacute bacterial endocarditis of aortic and mitral valves, superimposed on old rheumative valvular disease. An infected clot in the left Sylvian artery had produced focal acute arteritis and necrosis of the vessel wall with aneurysmal dilatation, resulting in hemorrhagic infarction of the temporal cortex and hemorrhage into the adjacent subarachnoid space (figure 1).

Case 3. An 18 year old colored girl had suffered from rheumatic heart disease since the age of six. One week prior to admission she developed swollen painful joints, followed by vomiting and stiff neck. On admission the heart was enlarged, with an apical systolic murmur. Neurologic examination showed only nuchal rigidity. Blood cultures were positive for *Streptococcus pyogenes.* Several days after admission the patient had a severe chill and became confused and disoriented. Spinal fluid was bloody and under increased pressure. She made a good recovery and the spinal fluid

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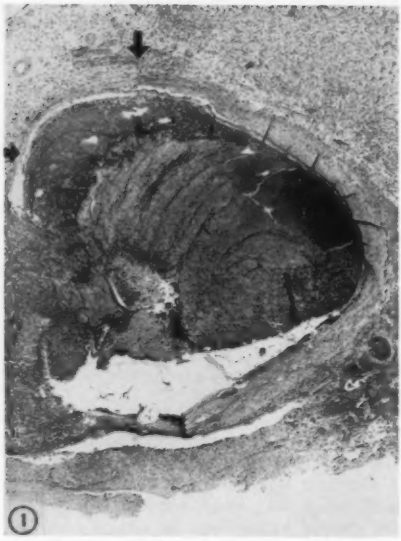

FIG. 1. *Case 2.* Mycotic aneurysm of Sylvian artery. The vessel contains an infected clot. Focal arteritis with bulging of the necrotic wall is shown between arrows.

became clear within a week. One month later she suddenly vomited and became unconscious in a state of decerebrate rigidity from which she did not recover. The spinal fluid was again bloody.

Mitral insufficiency with destruction of the mitral cusps was found at necropsy, associated with foci of metastatic nephritis. The brain presented both recent and organizing hemorrhage into the basal cisterna, with a terminal massive intracerebral hematoma. The source of bleeding was a typical narrow-necked saccular or berry aneurysm located at the bifurcation of the middle cerebral artery in the Sylvian fissure and invaginating into the uncus (figure 2). Study of the neck of the sac demonstrated characteristic disappearance of media and internal elastica at its origin from the wall of the artery (figure 3). Inflammatory reaction in this region was limited to occasional migration of leukocytes from the contained clots. The fundus, however, showed almost complete necrosis of the wall, with infiltration of both this portion of the sac and the adjacent brain tissue by neutrophils, forming an acute abscess.

Case 4. A 44 year old white man was admitted unconscious with complete left hemiplegia and a dilated, fixed pupil on the right. There was history of a previous cerebrovascular accident several years before, from which he had recovered completely. Shortly after admission the neck became rigid. Spinal fluid was clear and under normal pressure, but contained 165 white blood cells. The next day the patient's condition deteriorated and both optic disks became elevated. The spinal fluid at this time was xanthochromatic with 780 white blood cells (77 per cent neutrophils), and later it was grossly bloody and under increased pressure. The patient ran an irregular type of fever until his death four days after admission.

At necropsy, chronic rheumatic valvular dis-

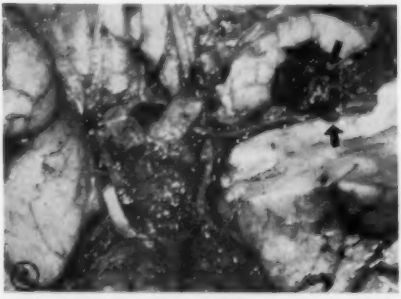

FIG. 2. *Case 3.* Arrows point to leaking "congenital" aneurysms of middle cerebral artery. The temporal lobe has been cut to show aneurysm embedded in an organizing clot within brain tissue.

FIG. 3. *Case 3.* Disappearance of medial coat and internal elastic lamina at neck of aneurysm (arrows). Note atheromatous plaque in the wall of the aneurysm.

ease was present, with superimposed subacute bacterial endocarditis. Massive, partially clotted hemorrhage distended the basal cisterns of the brain. The source of bleeding was a saccular aneurysm arising at the bifurcation of the basilar artery (figure 4). The aneurysmal sac was filled with organizing blood clot and had compressed and eroded the floor of the third ventricle, the hypothalamus, and the cerebral peduncles. The entire wall of the sac was necrotic and infiltrated with neutrophils. In addition, one posterior cerebral artery at its origin from the sac contained a partially organized, septic clot which had caused a focal acute arteritis (figure 5). The subarachnoid space contained both hemorrhage and inflammatory cells. Brain tissue immediately adjacent was infiltrated with hemorrhagic and inflammatory elements.

COMMENT

Four cases are reported in which subarachnoid hemorrhage from a ruptured aneurysm occurred during the course of subacute bacterial endocarditis. In all instances, rupture of the aneurysmal sac resulted from complications of the intravascular infection, but in only two (cases 1 and 2) was the aneurysm itself of mycotic origin.

The term mycotic aneurysm was introduced by Osler[1] to describe focal aneurysmal dilatations of the arterial wall encountered in infections arising within the vascular system. Eppinger,[2] who conducted extensive studies on this subject, considered such lesions the result of lodgement of an infected embolus in the vessel wall, with the production of focal acute or subacute arteritis and consequent bulging of the weakened vessel at the site of embolism. This type of aneurysm in subacute bacterial endocarditis was originally described in the aorta, but has since been reported in both the systemic and cerebral arteries.

The role of mycotic aneurysm of the circle of Willis as a causative factor in subarachnoid hemorrhage is difficult to

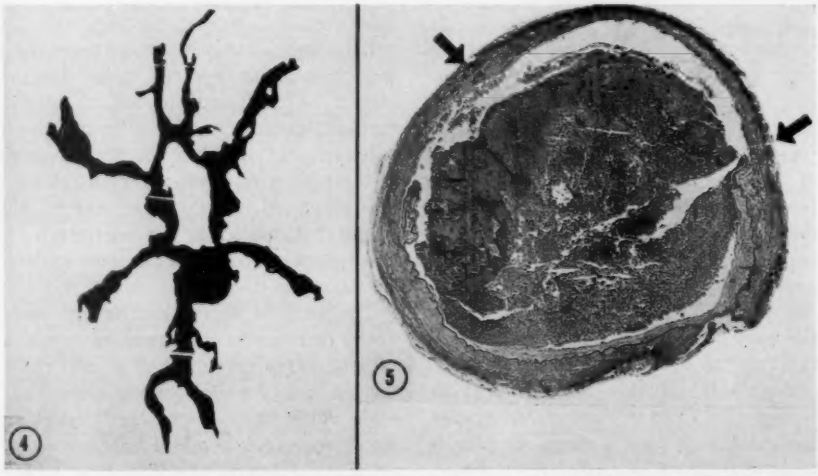

FIG. 4. *Case 4.* Circle of Willis. The basilar artery terminates as a saccular aneurysm, with both posterior cerebral arteries arising from its sac.

FIG. 5. *Case 4.* Posterior cerebral artery distal to its origin from the aneurysm. The lumen is filled with an infected clot. A portion of the wall shows arteritis and necrosis (arrows). Similar changes were present in the entire sac of the aneurysm.

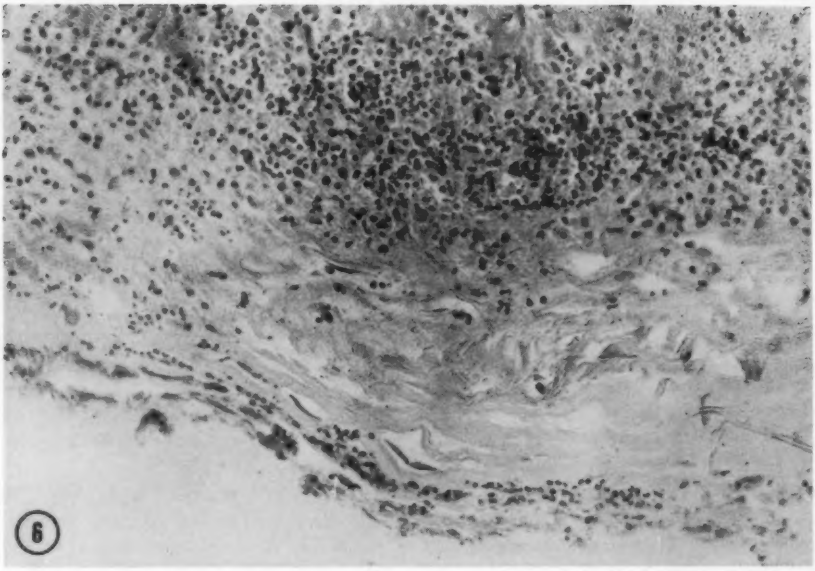

FIG. 6. Fundus of a "congenital" aneurysm approximately one week after onset of leakage. Inflammatory elements are present in the clot within the sac and infiltrate the disintegrating wall. No evidence of subacute bacterial endocarditis or systemic infection was found at necropsy.

evaluate. This is particularly true of cases published before the work of Forbus,[3] Richardson and Hyland,[4] and Bremer[5] gave impetus to the study of the "congenital" berry or saccular aneurysms of the cerebral vascular tree. Relatively few early reports[6] are sufficiently well documented to permit unqualified acceptance of the diagnosis of mycotic aneurysm. Frequently histologic studies are not reported and the description of the aneurysmal sac, its size, and location are at variance with the explicit criteria established by the original investigators. Even in more recent studies, the validity of such a diagnosis may in some instances be open to question. Hamby[7] has indirectly voiced this opinion by pointing out that the incidence of mycotic aneurysm as the cause of subarachnoid hemorrhage is remarkably higher in some reported series than in others. Mitchell and Angrist[8] considered mycotic aneurysms to be the source of subarachnoid bleeding in 28 per cent of their 36 cases, while a similar etiology was identified in only 3 per cent of Albright's[9] 32 patients. No aneurysms of this type were found in 96 cases studied by Courville.[10]

The lack of agreement on the incidence of mycotic aneurysms of cerebral vessels undoubtedly stems in part from the absence of uniform criteria for diagnosis. Some authors apparently consider coexistence of a cerebral aneurysm and subacute bacterial endocarditis tantamount to establishing the mycotic origin of the cerebral lesion.[11] This concept, however, does not take into considera-

tion the possibility that "congenital" or saccular aneurysms may already exist on the cerebral vascular tree of individuals who later develop intravascular infections. Aneurysms of this type could be demonstrated in 131 (9.8 per cent) of 1,335 consecutive specimens studied at necropsy at the Philadelphia General Hospital.[12]

Another factor which may contribute to misinterpretation of the origin of cerebral aneurysms is failure to evaluate the significance of inflammatory reaction in the sac wall after leakage has occurred. Not infrequently at this stage, the lumen of a saccular aneurysm may be filled by a clot largely composed of neutrophilic leukocytes. These elements, at times intermingled with mononuclear cells and phagocytes, frequently migrate into the wall of the sac and infiltrate its structures (figure 6). The reaction is apparently akin to that seen in early cerebral infarction where, as result of stasis, transport of neutrophils occurs through the walls of capillaries and smaller arterioles. It is doubtful, however, whether this type of inflammatory reaction is to be interpreted as indicative of intravascular infection, especially in the absence of clinical or necropsy confirmation. In the presence of subacute bacterial endocarditis, as in cases 3 and 4 of this series, the possibility that septic embolism may occur in the wall of a preformed "congenital" aneurysm cannot always be ruled out. Under such conditions the size of the aneurysm, the presence of remnants of a collagenous sac wall, and the characteristic anatomic structure of the neck of the lesion should be sufficient to establish the nonmycotic origin of the aneurysm. Review of necropsy studies in 175 cases of subarachnoid hemorrhage associated with cerebral aneurysm at the Philadelphia General Hospital revealed that subacute bacterial endocarditis was present in seven (4 per cent). In only two (cases 1 and 2 of this series), however, could a mycotic origin of the aneurysm be demonstrated.

SUMMARY

Four cases of subarachnoid hemorrhage associated with subacute bacterial endocarditis have been presented. In two, the source of bleeding was a true mycotic aneurysm, and in two, a "congenital" aneurysm with superimposed necrotizing arteritis of the sac wall was responsible. The role of mycotic aneurysms in subarachnoid bleeding associated with subacute bacterial endocarditis is discussed.

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Permeability of Cerebral Blood Vessels Studied by Radioactive Iodinated Bovine Albumin

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HISTOLOGIC EXAMINATION of the brains of experimental animals which have undergone convulsive seizures shows evidence of tissue damage which, to some extent could be the result of increased vascular permeability. Diapedesis of red cells, edema, and nerve cell damage in the acute stages, and perivascular hematogenous pigment, nerve cell deficit, and gliosis around the blood vessels in chronic conditions are examples of such changes.[1–5]

Other workers obtained more direct evidence by experiments in which trypan blue was used to test the permeability of the blood-brain barrier in various pathologic conditions, including electrically-induced epileptic seizures. Bjerner and co-workers,[6] using trypan blue, has shown that epileptic seizures produce a change in the blood-brain barrier, resulting in a blue staining of the nervous tissue. In his work, and in that of numerous other investigators, substances used to test the permeability of the blood-brain barrier were of relatively small molecular size. Therefore, we have thought that new information might be obtained by using a substance of large molecular size, and we took as our first problem the study of the permeability of the cerebral blood vessels to radioactive iodinated bovine albumin. We felt, also, that any light thrown on properties of the blood-brain barrier in relation to molecules of proteins might be of value for better understanding of those disorders which may be related to antigen-antibody reactions.

The second problem which we wanted to investigate was the mechanism of cerebral lesions resulting from status epilepticus, a possible cause of infantile hemiplegia. It is known that cortical lesions in this disease are particularly severe in the depths of the sulci.[7] We postulated that lesions resulting from status epilepticus are due, at least partly, to breakdown of the blood-brain barrier. To test this hypothesis, we produced a series of electrically-induced epileptic seizures in experimental animals in such a way as to imitate human status epilepticus, and studied the distribution of changes in permeability, particularly in relation to the cerebral cortex.

MATERIALS AND METHODS

All experiments were carried out on cats weighing from 1.8 to 2.6 kg. The

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exact age of the animals was unknown, but old or debilitated animals were not used. Both sexes were used.

The seizures were induced with a standard clinical electroshock machine, and usually 80 volts in 0.3 seconds were sufficient to induce a major epileptic seizure. However, a variable proportion of the seizures induced with this intensity of electrical current, especially in the later stages of the treatment, were of an atypical or abortive type characterized by the absence of tonic phase or postconvulsive coma. Round brass electrodes which measured 1.5 cm. in diameter were applied in front of the ears after the hair was clipped and the skin was rubbed with electroencephalographic jelly. The convulsive seizures were induced in nonanesthetized animals. In those procedures requiring anesthesia, Nembutal, 0.05 gr. per kg. body weight, was used.

The iodinated (I^{131}) bovine serum albumin was prepared, using a modification of the method published by Gilmore and co-workers.[8] The albumin was suspended in normal saline and the intensity of radiation was such that approximately 3 to 6 cc. corresponded to one millicurie. Not more than 2 per cent of the total radioactivity could have been due to unbound iodine. The albumin was injected intravenously, usually before the electroshocks were administered unless stated otherwise, and approximately one millicurie was used in each individual experiment.

In order to eliminate the radioactive blood from the vessels of the brain, the following procedure was adopted. At the end of the experiment, the abdomen of the animal was opened under anesthesia and the inferior vena cava was cannulated at the level just distal to the entrance of the renal artery. The abdominal aorta was clamped at approximately the same level. One of the plasma substitutes, Dextran or Subtosan, was injected through the cannula into the venous circulation at the rate of 100 drops per minute. At the same time the right external jugular vein was cut, its proximal end was clamped, and the distal stump was left open to let the animal bleed. Exchange transfusion was carried on until the animal's heart stopped beating. At this time, usually about 30 minutes, blood-tinged plasma substitute was running from the sectioned jugular vein, while all the mucous membranes and internal organs were very pale. The average amount of plasma substitute used for one animal was 200 cc. The brain was then perfused through both cannulated carotid arteries with 100 cc. of Elliott's solution at a hydrostatic pressure of 120 cc. of water. This was followed by perfusion with 150 cc. of a mixture of 20 per cent formalin and 20 per cent alcohol in normal saline. The brain was then removed and left in the same fixative for 12 hours. After that time the brain was cut coronally at 0.4 cm. intervals and examined grossly. Representative frozen sections, 100 microns thick, were mounted on glass slides and left to dry for two hours.

When the sections were completely dried, they were placed into apposition with either Kodak medical x-ray "No-Screen" films or with Kodak autoradiographic "No-Screen" plates, top-coated, emulsion thickness 25 microns. The exposure time was 72 hours. The emulsions were developed and fixed in the usual manner.

After the autoradiographic exposure, the same frozen sections which were used for autoradiography were stained

by Alexander's benzidine technic and counterstained with 0.5 per cent solution of basic fuchsine. Microscopic examination of these slides showed absence of blood in the cerebral vessels of both the experimental and control animals. As controls, we used animals which had been injected with iodinated albumin and either killed by the exchange transfusion or killed by overdose of Nembutal without perfusion. In the first group, the autoradiographs showed no radioactivity in the brain and meninges and a slight radioactivity in the choroid plexus. In the second group, there was strong radioactivity over all large and medium-sized cerebral and meningeal vessels and a diffuse radioactivity over the tissue in general, more pronounced in the gray than in the white matter.

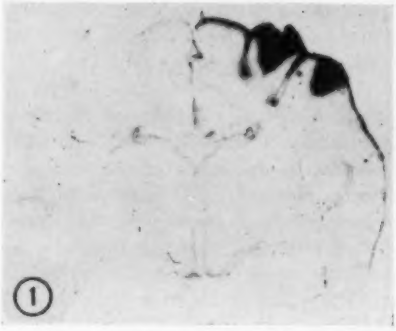

FIG. 1. Autoradiograph showing the lesion produced by application of heat to the skull. Note two wedge-shaped areas of radioactivity in the adjacent gyri.

RESULTS

Two relevant preliminary experiments are first described.

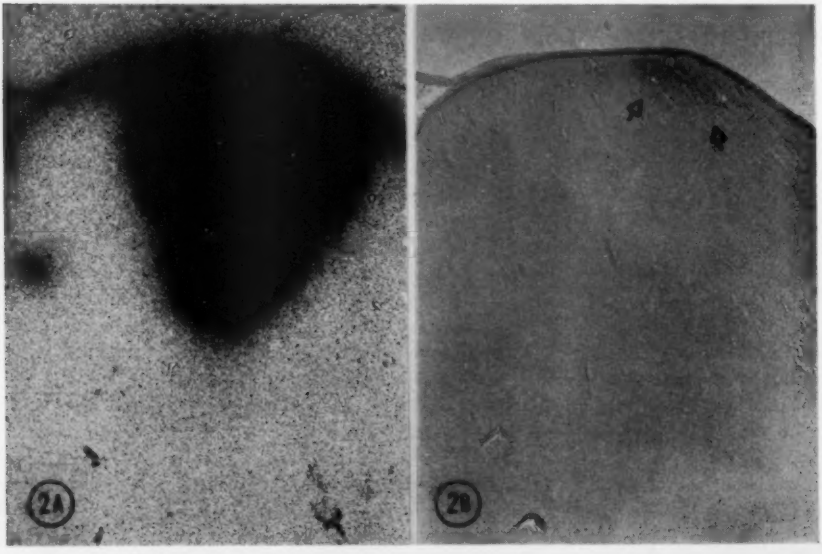

FIG. 2. *A*. The lateral wedge-shaped area of radioactivity from figure 1 under higher magnification to compare with *B*, the histologic section from which the autoradiograph was obtained. Benzidine method counterstained with acid fuchsin. Note the absence of red blood cells. A small area of necrosis is marked with arrows. The magnification of both *A* and *B* is the same.

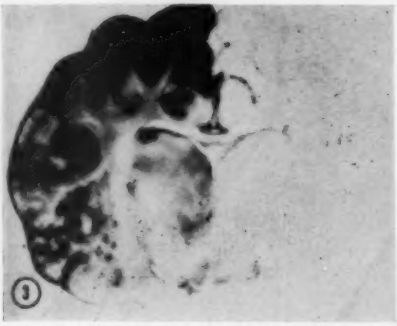

FIG. 3. Autoradiograph showing the lesion produced by injection of air into the left common carotid artery. Note intense radioactivity in the hemisphere on the side of air injection, predominantly in the cerebral cortex.

Experiment 1

The purpose of this experiment was to study the permeability changes induced by heat necrosis. One cat was injected intravenously with one millicurie of iodinated bovine albumin. Half an hour later, a brass rod about 1.5 cm. in diameter, whose end was shaped to fit the surface of the skull, was heated in the gas burner and applied to the exposed skull under anesthesia for one minute. Half an hour after the application of heat, the animal was killed by the exchange transfusion technic. The radioautographic result obtained in this experiment is shown in figure 1. There are wedge-shaped strongly radioactive areas in two adjacent gyri. Comparison with the histologic section shows that no blood was left in the vessels except in the very small superficial necrotic area. The histologic study of the tissue underlying the region of intense radioactivity shows no evidence of tissue damage, with the exception of the above-mentioned superficial necrosis which occupies an area much smaller than that of intense radioactivity (figure 2).

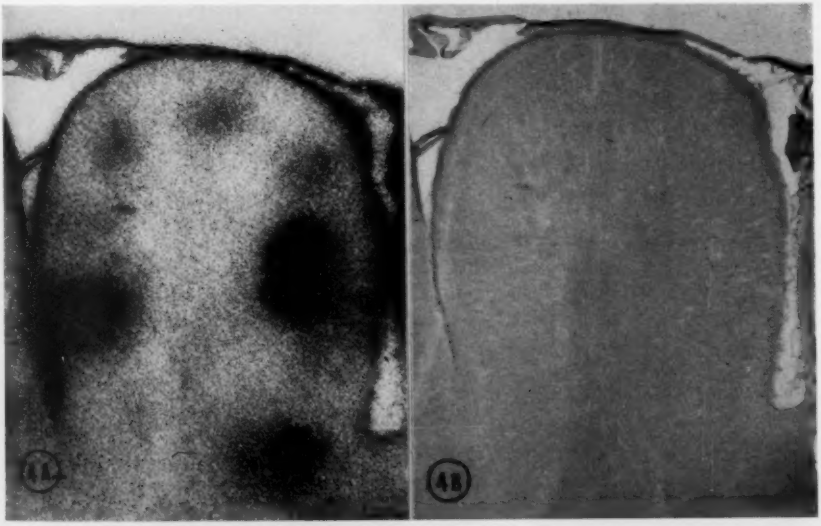

FIG. 4. *A*. Autoradiograph after air embolism. Enlarged picture of one convolution to show the pattern of radioactivity and to compare with *B*, the histologic section from which this autoradiograph was obtained. Benzidine method counterstained with acid fuchsin. Notice absence of red blood cells.

Experiment 2

The purpose of this experiment was to study the change in permeability resulting from air embolism. In anesthetized animals one millicurie of iodinated bovine albumin was injected intravenously. Half an hour later the right common carotid artery was exposed and injected with 0.3 cc. of air three times at 30-minute intervals. Half an hour after the last air injection, the animals were killed by exchange transfusion. Grossly the brains were unremarkable. The autoradiographic pattern obtained is shown in figure 3. There is patchy and confluent radioactivity over the whole hemisphere on the injected side. The radioactivity is present in the basal ganglia and in the cortex, but is more pronounced in the latter. Close examination of the areas of darkening of the photographic emulsion and a comparison with the histologic slides shows that the individual areas of radioactivity are related to blood vessels of precapillary size. The benzidine stain of the histologic slides shows that the blood vessels are free from blood (figure 4) and that the individual patches are 10 to 15 times larger than the diameter of the corresponding blood vessels. The radioactivity in the center of each individual area of darkening is more intense in the center and fades away toward the periphery. Comparison of this autoradiographic pattern with that obtained in the nonperfused brain (figure 5) shows that the patches of radioactivity related to the blood vessels in the latter are two to three times larger than the diameter of the corresponding vessel, and that the edges of the darkened areas are much sharper.

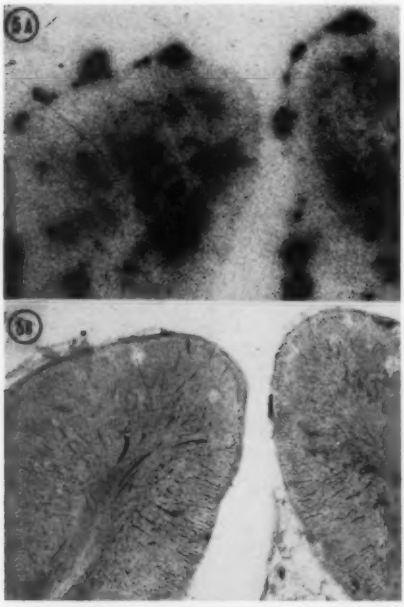

FIG. 5. *A*. Control autoradiograph. The animal was injected with iodinated albumin, but the brain was not perfused. Note intense radioactivity in circumscribed small areas. *B*. Histologic section from which this autoradiograph was obtained shows the blood vessels filled with red blood cells. Benzidine method counterstained with acid fuchsin. Compare *A* with *B* and note that the radioactive areas correspond to the blood vessels.

Experiment 3

The purpose of this experiment was to study the permeability changes resulting from electrically-induced convulsive seizures. Unless otherwise stated, 60 seizures were induced over a period of six hours.

In the first group of ten animals, the seizures were produced half an hour after the intravenous injection of radioactive albumin. The animals were killed by exchange transfusion half an hour after the last seizure.

The autoradiographic pattern was similar in all animals. There was symmetric radioactivity in the thalamus and hypothalamus (figure 6) and a lesser concentration of radioactivity in the cor-

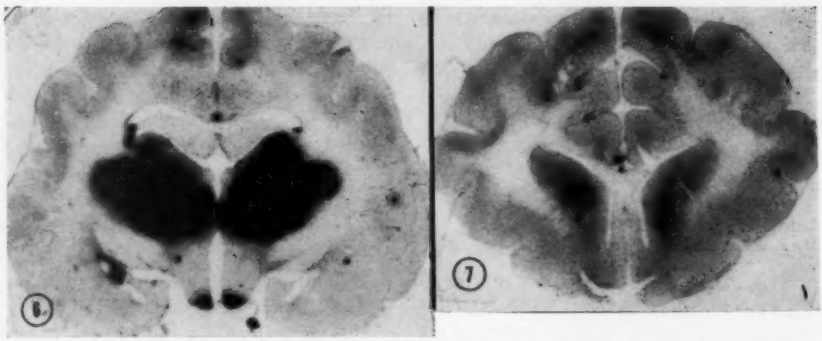

FIG. 6. Autoradiograph of a brain section from an animal subjected to 60 electroshocks during six hours. Note the intense radioactivity in the thalamus and the hypothalamus. It is less intense in the cortex.

FIG. 7. Autoradiograph of a brain section from an animal subjected to 60 electroshocks during six hours. Note the radioactivity in the caudate nucleus and, to a lesser extent, in the cortex.

tex and the striatum (figure 7). The darkening of the photographic emulsion was diffuse and no relation to blood vessels could be seen. In the thalamus comparison of autoradiographs with histologic section (figure 8) showed that radioactivity varied from one thalamic nucleus to another but remained bilaterally symmetric. The regions affected most prominently were the anterior thalamic nuclei, the nucleus medialis dorsalis, the nucleus ventralis posterior, and the pulvinar. The lateral geniculate body was very prominently affected in some animals, but less so in others. The same applied to other thalamic regions in which there was considerable variation in the intensity of radioactivity from one animal to the other. Among the other subcortical gray masses, the zona incerta and the substantia nigra were affected to a moderate degree. The hypothalamus was radioactive in all cases. No serial sections through the hypothalamus were available, but it was evident that the tuber cinereum was affected constantly. The radioactivity of the striatum varied from one animal to another, and the picture represented in figure 7 is taken from the animal whose

FIG. 8. *A*. Histologic section of the thalamus and *B*, autoradiograph of the same. The animal was subjected to 60 electroshocks during six hours. Note the intense radioactivity in the lateral and medial geniculate body, putamen, nucleus ventralis posterior, and the substantia nigra.

response was particularly marked. In the cortex the radioactivity was diffuse, but in certain animals it was noticed that increased radioactivity was present in the depths of the sulci (figure 7). In the lower brainstem no radioactivity was present. In most animals there was slight radioactivity in the cerebellum which was usually more intense in the vermis.

The influence of the number of seizures on the intensity of the radioactivity was investigated in another group of six animals. It was found that the same pattern could be seen after ten seizures and that it increased in intensity with the number of induced seizures.

In one animal the radioactive albumin was injected immediately after a series of 60 seizures and the cat was killed by exchange transfusion three hours later. In this animal no radioactivity was present in any part of the brain with the exception of the tuber cinereum.

Experiment 4

The purpose of this experiment was to investigate whether generalized brain edema or generalized venous congestion would produce the autoradiographic pattern similar to that obtained after electrically-induced seizures. Brain edema was produced in one animal, which had been previously injected with labeled serum albumin, by intravenous infusion of 250 cc. of 1.1 per cent solution of glucose over a period of one and one-half hours at the rate of about 40 drops per minute.[9] During this experiment the dura was exposed on one side, and toward the end of the injection of the hypotonic solution, it was observed that the brain was bulging through the bony defect. An autoradiograph of this animal showed only small patchy areas of radioactivity underlying the herniation of the brain and corresponding to minute petechial hemorrhages. No radioactivity was observed in other regions.

Two animals were used to test the effect of venous congestion. In the first the internal jugular veins were ligated permanently. The external jugular veins were clamped for one-minute periods at intervals of two minutes. This procedure was repeated 60 times. A half-hour period of rest was interposed in the middle of this procedure. In the second animal all jugular veins were clamped for 30 minutes. During the first ten minutes of the experiment, the animal received a slow injection of 1 cc. of 1:1000 solution of epinephrine diluted in 5 cc. of saline. In both animals the autoradiographs were negative.

Experiment 5

This was a control experiment to test whether or not the autoradiographic pattern obtained after seizures could be due to unbound iodine. Since, according to the manufacturer, the maximum amount of unbound iodine was 2 per cent and the amount of radioactive protein injected was equal to one millicurie, in each individual experiment no more than 20 microcuries of radiation would have been due to the unbound iodine. It was decided to inject double that amount; 40 microcuries of standard oral solution of potassium iodide (I^{131}) were injected intravenously and 60 electroshocks were induced as usual. The result of this experiment was entirely negative. There was no radioactivity in the brain.

DISCUSSION

Under the conditions of our experiments, no radioactivity was present in the brains of control animals which lived for six hours after the injection of one

millicurie of iodinated bovine serum albumin. The only exception was the choroid plexus which was slightly radioactive. Whether this was due to the presence of radioactive material in the tissue itself or to the presence of a minute amount of blood not completely washed out by perfusion technic was not determined.

In the experiment with heat necrosis, diffuse and intense radioactivity indicated that both wedge-shaped areas had been permeated by blood plasma, though no evidence of more intense blood vessel damage, resulting for instance in diapedesis, was seen. The size of the lesion which showed intense radioactivity was much larger than the area of actual necrosis. We cannot say whether a certain amount of damage to the tissue showing intense radioactivity could have been demonstrated with other staining methods, but comparison of the sections stained with basic fuchsin with the autoradiograph indicates that this last method may be much more sensitive for the detection of minimal changes in physical-chemical properties of the tissue.

The two wedge-shaped radioactive areas in the adjacent gyri were separated by a tissue which was not radioactive. However, both these areas and the separating tissue were all underlying the surface of the brain to which heat had been applied. The shape of the lesions and the presence of separating nonradioactive tissue indicated that, in addition to pure physical transmission of heat from the bone, there are some other mechanisms responsible for the production of this effect.

The autoradiographic pattern obtained after air embolism suggested that there were multiple regions of blood vessel damage, mostly at the precapillary level. They were randomly distributed but more numerous in the cortex. Broman,[10] using the trypan blue method, showed that air embolism produces damage to the cerebral blood vessels at the precapillarly level, and our results indicate that this damage could be severe enough to allow the passage of large molecules such as proteins through the vessel wall. The absence of blood in the vessels and the size of individual patches of radioactivity, which were many times larger than the corresponding blood vessels, together with the peripherally-decreasing intensity of radioactivity, indicate that the radioactive material penetrated the blood vessel wall and was actually located in the tissue. It may be pointed out that the histologic sections in this experiment were unremarkable, and the autoradiographic method clearly showed changes which were not observable on the chromatic stain used.

The autoradiographic pattern obtained after electrically-induced seizures was both unexpected and remarkable. Two separate problems can be considered in connection with these results.

The first is the exact histologic localization of radioactivity in relation to various tissue elements. Since it was shown by the benzidine technic that no blood remained in the capillaries and the larger blood vessels, the only possible localization for the radioactive proteins is either in the walls of the vascular tree or outside of it in the tissue itself or both. Since the pattern of the blood vessel was not reflected in the autoradiograph and since the intensity of the radiation was rather strong, the walls of larger blood vessels at least could be excluded as the possible site of the concentration of radioactive protein. However, it was observed in several instances

that the wall of the empty anterior cerebral artery was definitely radioactive, whereas the walls of other arteries of comparable size remained inactive. At present we cannot offer any explanation for this phenomenon. It is still possible that the endothelium of all capillaries in the afflicted areas concentrates radioactivity under the condition of repeated epileptic seizures. If all the capillaries contained a certain amount of radioactive proteins in their walls, the diffuse pattern observed in our autoradiograph could be obtained, considering that our sections were rather thick and that the resolution of the autoradiograph was poor. The second possibility is that the radioactive plasma permeated the blood vessel wall and penetrated into the tissue itself outside of the capillaries, with or without additional presence in the endothelium. Which of these two theories is correct is impossible to answer without further work with thinner sections and better autoradiographic resolution. It may be added, however, that the two explanations may be not so mutually exclusive as it seems at first. It has been suggested that damage of the endothelium, as evidenced by the stainability with trypan blue, is the first stage of increased impairment of the normal function of the blood-brain barrier.[11] The same might apply to the imbibition of plasma proteins by the vascular endothelium.

The second problem is why the radioactivity was concentrated in the thalamus. This touches obviously upon the question of why epileptic seizures produce changes in vascular permeability at all. Our experiments with brain edema and congestion seem to indicate that purely mechanical or vasomotor phenomena do not impair the blood-brain barrier to such an extent as to cause the leakage of molecules of protein size. It can be speculated that, under the influence of repeated seizures, there is considerable accumulation of certain metabolites[12,13] which, if the seizures follow in close succession, may attain such concentration as to be damaging to the tissue. If this hypothesis is correct, we must assume that the thalamus under our experimental condition was the site of more active metabolism and was exposed to greater damage than the cerebral cortex. It is particularly interesting to mention the results of experiments of Jung[14] in which he showed that, in atypical and abortive seizures in cats, the predominant electrical activity was in the thalamus and not in the cortex. Peters and Vonderahe[15] pointed out recently that the anatomic substrate for the electrically-induced epileptic seizures has to be sought, not in the cortex but in the subcortical regions such as the thalamus and the reticular formation. They came to this conclusion by the observation of electrically-induced seizures in the salamander. The basic pattern of the seizure in this animal is strikingly similar to that of man or cat, in spite of the fact that the salamander does not possess a cerebral cortex.

No explanation can be given for the varying intensity of radioactivity in various thalamic nuclei. Possibly it may be related to some extent to the vascularity of these various regions.

The experiment in which radioactive protein was injected immediately at the termination of the seizures indicated that whatever changes might take place during the seizures must be reversible and the reversion to normal must follow immediately after cessation of the seizures.

The control experiment with unbound iodine indicated that it was not responsible for the autoradiographs obtained in our experiments.

SUMMARY

1. Permeability of the blood-brain barrier to iodinated (I^{131}) bovine serum albumin was investigated in cats in relation to heat necrosis, air embolism, electrically-induced seizures, passive congestion, and brain edema.

2. Under normal conditions the blood-brain barrier was impermeable to the bovine serum albumin.

3. Heat injury produced an autoradiographic pattern which indicated that the plasma proteins permeated the tissue in an area larger than that in which necrosis was seen histologically.

4. Air embolism produced severe breakdown of the blood-brain barrier for the molecules of albumin at the level of the precapillaries.

5. Sixty electroshocks induced over a period of six hours produced radioactivity which was intense in the thalamus and hypothalamus and less intense in the striatum and the cortex.

6. The radioactivity varied from one thalamic nucleus to another, but certain thalamic nuclei were constantly affected more than others.

7. It was suggested that the autoradiographic pattern resulting from convulsions was due either to the lodging of radioactive proteins in the endothelium of the capillaries or to actual passing of the proteins through the blood vessel wall into the tissue. The reason for predominant localization in the thalamus has been discussed.

8. Edema and passive congestion did not produce enough blood vessel changes to result in concentration of radioactivity in the tissue.

9. A control experiment with unbound iodine indicated that the results were not due to unbound iodine, which contaminates iodinated proteins to some extent.

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CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Charles D. Aring, M.D. and Joseph Smith, M.D.*

CASE PRESENTATION

A 70 year old, right-handed Negro man, an unemployed railroad laborer, had had generalized seizures since 1938. At first they occurred once a year, then increased in frequency until they were occurring every few weeks in 1942. He had been in a state hospital for epileptics in 1941, but had signed his own release because it was too confining. In 1942 electroencephalographic studies showed a diffuse, non-specific, cerebral dysrhythmia and an air encephalogram indicated generalized mild cerebral atrophy. Cerebrospinal fluid study was normal. His past medical history contained no other leads. He had sustained a fracture of the left femur in an accident in 1925. He did not use alcohol excessively. From 1949 to 1954 the patient was treated in our urology clinic for urethral strictures; he had no convulsions during this period.

The patient was brought to the hospital on January 3, 1955 following a seizure. He was promptly put on Dilantin and phenobarbital, both in 0.1 gm. doses three times daily. He was completely oriented; he was weak and incontinent. On the ward he had repeated seizures which involved the left limbs and left side of his face without any change in consciousness. On occasion the attack spread to involve all of the extremities, but he retained consciousness nevertheless. Sometimes the head would turn to the left in these attacks. The patient said that this type of seizure had been occurring irregularly for the past year.

Over the period of a week the seizures became less frequent and less severe. After the seizures diminished, a left homonymous hemianopia and a slight left lower facial weakness were noted. Deep reflexes were hyperactive and equal. Sometimes he had clonic jerking of the limbs, particularly on the left; some of the descriptions in the patient's record characterized the involuntary movement as "tremor." The patient had great trouble walking; his gait was weak and wide-based, but this improved as the seizure activity became less until his discharge on January 13, 1955.

He promptly went off medication. When seen in the neurologic clinic on January 17, 1955, he was alert and cheerful and getting about without trouble. No hemianopia could be demonstrated. He had had no seizures of any sort after leaving the hospital.

On February 23, 1955 he returned to the hospital because of recurrence of gross jerking movements of the left limbs. He was quite alert and cooperative, although he sometimes became confused at night. He said that the difficulty began in the left limbs shortly after attending the neurologic clinic in January, and again he reported some mild left-sided jerking intermittently for about a year. Continual and partial epilepsy involved the muscles of the left limbs, thorax, and abdomen; the twitching was regular at a rate of about 85 to 100 per minute. The frequency increased when the left limbs were stimulated. There was great weakness of the left limbs. He did not seem to be able to lift them from the bed, although the hand and fingers could be moved clumsily and the grip varied in strength, becoming weaker during the increased intensity of the clonic movement. There was left hemianopia. Between twitches it was possible to get the deep reflexes, the plantar responses were flexor, and there was no Hoffmann response.

From Cincinnati General Hospital, Cincinnati, Ohio.

The following abnormalities were recorded in the general physical examination. There was maximal arteriosclerosis of the peripheral vessels and arteriosclerotic changes in the fundi. The prostate gland was hypertrophied, large, firm, and movable; inguinal lymph nodes were found on both sides.

He was given Dilantin, 0.1 gm. three times daily. Both Dilantin and phenobarbital were used during the remainder of his life; the dosage of Dilantin was raised as high as 0.9 gm. on April 19, and that of phenobarbital to 0.4 gm. on May 27. A variety of barbiturates were given parenterally in attempts to halt the convulsive activity. Twitching gradually diminished in intensity until March 5, at which time it disappeared completely. He got out of bed in early March and began getting about in a walker on March 25. If he became anxious, slight twitching recurred in the left upper arm.

He was transferred to the hospital for chronic diseases on March 28, 1955. There the neurologic examination was normal, with the exception of periods during which small twitching movements occurred involving the left fingers, hand, and forearm. These were rhythmic and somewhat reminiscent of "pill-rolling." The strength in the left limbs remained good. On April 13, 1955 the left hemianopia was again noted. A gross pill-rolling tremor and astereognosis were described in the left hand. He had become unable to walk, although the strength in his limbs remained good.

An air encephalogram was done on April 15, 1955. Three days later he developed convulsive movements of moderate degree in the face and in the upper extremities and became somewhat unresponsive. He was given 250 mg. of sodium Amytal intravenously, which quieted the involuntary activity except for clonic twitching which remained in the left hand. He was rather lethargic and had great difficulty swallowing. A nasal feeding tube had to be inserted. The left upper extremity became weak and rather toneless. He was incontinent of urine and feces. By April 20 he had improved so that he talked, but he remained incontinent. He had only occasional twitching in the left hand and even less frequent twitching of the left side of the face. He remained in this state until May 28 when he became unresponsive. A coffee-ground material began to exude from the nasal tube, at which time his blood pressure was 80/60, pulse 112, and respirations 40. He perspired profusely, and his extremities were cold. The abdomen was distended. He died on May 29, 1955.

There were four negative Wassermann and gold curve determinations.

Two electroencephalograms were done in April 1942, a week apart. Both records contained slow waves varying between three and six per second, some of high voltage, usually interspersed between low voltage and very fast activity. Also there were long runs of square-topped, medium voltage six per second waves. These abnormalities were present in all areas of the cortex from which recordings were made; in other words, there was no evidence of localization. The outstanding feature of electroencephalograms done on January 5 and March 3, 1955 was a moderate-amplitude, slow, spike pattern in the right occipital leads.

Roentgen studies on February 23 and 28, 1955 revealed an old fracture of the left femur with poor union. There was some cardiac enlargement. Skull films were entirely normal. A chest film on May 28, 1955 showed a somewhat enlarged heart and a hazy increased density throughout most of the right lung field. The flat film of the abdomen showed greatly dilated loops of small bowel.

In the pneumoencephalogram of April 15, 50 cc. of air were injected by the lumbar route. There was excellent visualization of the lateral and third ventricles, which were in the midline. Small amounts of air had travelled into the subarachnoid spaces over the vertex where no abnormality was seen.

The blood pressure determinations had ranged around 140/75 throughout his many hospital studies. After the collapse on May 28, fluid from the nasal tube was found to be guiac 4 plus. At that time the blood carbon dioxide was 16.8 mEq./L., chlorides 84.5 mEq./L., blood urea nitrogen 29 mg. per cent, and the pH 7.30. The blood hemoglobin was 15 gm. and the hematocrit 49. Many urinalyses in 1955 had indicated infection in the urine, with positive albumin tests and a moderate number of cells and specific gravities that ranged between 1.010–1.020.

Cerebrospinal Fluid

	Date	*I.P.*	*F.P.*	*Cells*	*Pr.*	*Sugar*	*Cl.*	*Culture*
L.P.	1942			0	31			
L.P.	1/3/55	170	125	2 RBC 2 WBC	30			
Pneumo	4/15/55			2 WBC	31			
L.P.	4/19/55	165	120	280 WBC	41	43	118	negative

DIFFERENTIAL DIAGNOSIS

DR. CHARLES D. ARING: Today we have a complex problem to unravel. Can the illness, beginning in 1938 at the age of 53 with generalized seizures, be related to the seemingly distinctive symptoms that might be thought of as the present illness, which had their onset in 1954 at the age of 69? As you know, seizures beginning at the age of 53 are unusual, and we will have to worry about them, as evidently was done in 1942. At that time the neurologic laboratory findings were within normal limits, except for the electroencephalogram which showed a non-specific cerebral dysrhythmia. The air encephalogram must have been normal, despite the note of generalized, mild, cerebral atrophy, because the second air study in 1955 was said to be normal. We know that an atrophied brain doesn't regenerate, so we can surmise that the first air encephalogram was normal, too. The cerebrospinal fluid also was normal. There is nothing in the initial paragraph of the protocol that leads me to any etiologic speculation, and we may pass on to attempt to localize the illness as described in 1954.

We learn that this man had been having seizures involving the left side of his body for a year prior to January 1955. No mention is made of weakness in 1954 during the year that he had suffered these attacks, the description of which sounds Jacksonian in type. We are not told whether they were followed by weakness; they may have been of the same type that he was known to suffer when he was on the wards here in 1955. I was among the clinicians who saw him in 1955 when he was having continuous seizures. These attacks, as far as I could tell visually, originated in no one spot in his anatomy. We know that the usual places for Jacksonian seizures to begin are the thumb and first finger, the corner of the mouth, or the big toe. These seizures were not initiated in that fashion. The muscles of his extremities and his face jerked all at once, as far as could be seen. So we don't have evidence that the seizures were firing from any one spot in the cortex, although this may well have been the case. In other words, we get no hint for localization from the description of the attacks, except that they were arising in the right hemisphere. Early in the course of these localized seizures we have no evidence that there was local weakness, such as one usually expects after repeated Jacksonian epilepsy. As was noted later in the protocol, this may have been a partial and continuous epilepsy. Partial and continuous epilepsy in some of its aspects should be differentiated from the usual Jacksonian fit. Described by Kojevnikov[1] in 1895 when it was termed "epilepsia partialis continua," one feature of this seizure is the absence of exhaustion paralysis so characteristic of ordinary Jacksonian epilepsy. Perhaps the reason for the lack of exhaustion paresis, or Todd's paralysis, may be the relative mildness of the discharge; the neurons do not seem to become refractory by reason of this repetitive and continual seizure. Whatever may be the case in this regard, it appears for the first year that this man had local seizures; he was not troubled by Todd's paralysis. This is an inference and I don't want to insist upon it; it is not mentioned in the protocol and, therefore, we infer that it was not a factor.

We get some hints for more exquisite localization from the later paragraphs of this protocol, where we find mentioned left hemianopia, left lower facial weakness, and still later astereognosis and tremor in the left hand. The tremor was termed pill-rolling in type. This allows us to define localization a bit better. For a time, the patient did not seem to have local weakness in the limbs. He was generally weak, particularly when asked to walk; his gait was described as weak and wide-based. His gait improved as his seizure activity became less; I would venture a guess it was likely that he got less sedatives as his seizures lessened, and this may have been the reason for his improving gait. I see nothing in the gait that gives any hint of localization whatsoever. I would attribute his trouble in walking not

particularly to local disorders of the brain, except perhaps secondarily, but I should think it was primarily due to whatever medication he was getting. We observe that when he went off medication, he got about without any particular trouble. In fact, he walked into the neurologic clinic in early January 1955, after being discharged from the hospital. Then he seemed to have had no localizing signs and no seizures despite his lack of medication.

In the February hospital admission, shortly after he appeared in neurologic clinic, we have a bit different picture because now we find the first mention of Todd's paralysis or exhaustion paralysis. The twitching was rhythmic and regular. It was at this time that I saw him and obtained no hints about finer localization by watching the seizures. The left hemianopia that had remitted was again present. We have the statement about an interesting phenomenon that I believe I observed – that certain stimuli to the limbs increased the rate or severity of the seizures. In other words, the threshold of certain cortical neurons might have been lowered since stimuli to the left limbs accentuated twitching, and indeed later it is mentioned that he was reasonably free of seizures except when he exhibited a certain amount of anxiety or fear. Therefore, these nerve cells were unusually accessible to certain stimuli, emotional and other, to which they should not have been. This helps us, I think, to put the lesion in the top levels of the brain.

Other aids to a more definite localization are the hemianopia and astereognosis, and, if he had it, the so-called pill-rolling tremor all on the left. Before we go any further, we might have some word about the final air encephalogram.

DR. ETHEL BLATT: Ventricular filling was good and the lateral and third ventricles were well outlined. There was no shift in the anteroposterior views. There might be interpreted a mild dilatation of the ventricles, probably the same as on the previous encephalogram. I would consider this a normal pneumoencephalogram, but someone might interpret it as mild cerebral atrophy.

DR. ARING: Since the electroencephalograms were of some aid in localization, would you tell us about them, Dr. Trufant?

DR. SAMUEL A. TRUFANT: As noted in the protocol, there was no significant localization in the electroencephalograms done in 1942. In one of them it was reported that there was a single short burst of activity which apparently arose in the right temporal region. Both of the electroencephalograms done in 1955 showed a spike pattern in the right temporo-occipital area. This was constant and showed little tendency to be reflected in other areas. Aside from this, the general tenor of the record was one of good organization. There was nothing to suggest any diffuse brain damage. One might have considered a surgical attempt to localize and remove a focus such as this.

DR. ARING: While these laboratory tests were a comfort to us, they must be put into another category as far as the patient is concerned. Indeed, I wonder whether the air encephalogram didn't result in his death, which has been the case in other aged people. I'll come back to this point again.

We have excellent evidence that this man was suffering from a localized cortical disease. With the minimal local weakness that he suffered in view of rather tremendous convulsive activity, it seems one might reasonably take the lesions away from the immediate vicinity of the rolandic fissure. The assist from the electroencephalogram would implicate the occipital lobe on the right. I would expect the right temporal lobe to be involved, since at one time he had a left lower facial weakness without any other evidence of local weakness. I tend to put the lesion in the superior temporal gyrus, because I suspect that the weakness which remitted was the result of a neighborhood lesion. I would believe the visual fibers may have been interrupted as they swing around the temporal horn of the lateral ventricle. The astereognosis picked up in one

of the final examinations would help us to localize the parietal lobe. So most of the trouble would appear to be post-rolandic. The only evidence that we have of cortical difficulty in the frontal area, it seems to me, is the mention, I think only once, that sometimes the head would turn to the left in attacks. This might represent spread of discharge from posteriorly lying foci in the cortex; I tend to exonerate the frontal areas from local lesion that could be picked up clinically. So I believe that this man had post-rolandic lesions specifically in the parietal, occipital, and perhaps temporal cortex. These are multiple, probably of varying age, and I would envision them as roughly wedge-shaped, their widest extent being at the cortex. They are likely to dip down into the subcortex, since they or their effects occasionally interrupt visual fibers, and a lesion may have extended as deeply as the basal ganglia to be associated with pill-rolling tremor. I would expect that these lesions are infarctions; I find no evidence for hemorrhage in the protocol unless it be terminal. The terminal state would seem to have been a secondary affair, within the purview of the so-called Cushing phenomenon. I think that he had upper gastroenteric bleeding and perhaps even ileus, since the roentgenograms late in May demonstrated dilated loops of bowel.

I want to spend a final few minutes on the nature of these lesions. We have enough evidence to make us reasonably certain that there was no localized mass lesion expanding within the cranium. We now know, since the work of the Massachusetts General Hospital group, that infarction and/or hemorrhage may be accompanied by seizures in a fair percentage of cases. Richardson and Dodge[2] studied 104 consecutive autopsy-proved cases of cerebral infarction and/or hemorrhage and seizures had occurred in 12.5 per cent. This compared with a control group of 74 cases of cerebral atherosclerosis without grossly visible brain lesions where only 2.7 per cent had seizures. The importance of their study in relation to our present case was that all cases with seizures had involvement of the cerebral cortex, whereas none of the patients with lesions confined to the subcortical structures had seizures. This is, of course, comforting corroborative evidence for the essential cortical nature of our patient's disease.

Why do people with cerebral infarction have seizures? Some of you may have heard Evans[3] describe his work on experimental occlusion of cerebral vessels. He found that where the blood supply was completely cut off to the parenchyma of the brain, there occurred a complete destruction of that parenchyma, finally with cyst formation if the animal was allowed to live long enough. In those cases in which there was only partial deprivation of blood supply, the neurons were devitalized and there occurred hypertrophy of certain glial elements. It has been considered that such partial deprivation of blood supply may somehow make for discharging lesions. It is known that people who have had analogous lesions in their cortex need not have seizures, so we are left with no explanation as to why seizures develop. We might fall back on the hypothesis that a certain percentage of the population has a seizure diathesis and that these are the people who have the possibility of developing epilepsy with an insult to their cortex; then epilepsy, whatever that be, is brought forth by the cortical lesion.

Now another word about the reaction to the air study. I think that the cerebrospinal fluid findings in the final tap are likely to represent a reaction to the air; we know that any foreign body put into the cerebrospinal fluid may induce meningeal reaction. It has been found, perhaps more of late than previously, that air studies are hazardous procedures in patients of advanced age. As I said before, while this study is a great comfort to physicians, I think that in the future we're going to have to rely more on clinical judgment and laboratory studies other than air to help us rule out mass lesions within the cranium.

Finally, what vessel or vessels might be

involved to produce these cerebral infarctions? Can we get any closer to the nature of the lesion? I think the process was atherosclerosis, and I would guess that some breakdown in the anastomotic system of the cerebral arterial circulation occurred. We hope that Dr. Smith will be able to tell us about the patency of the internal carotid arteries on the two sides; I wouldn't have much hope that he will tell us about the patency of the vertebral arteries. We now know that we must have this information in order to make any attempt to explain how and why infarctions occur in the brain. Adams and his group at the Massachusetts General Hospital[4,5] have directed our attention to the marvelous protection afforded the cerebral circulation by anastomotic vessels which are thrown into function when something happens to one or another artery to diminish blood supply to the brain. Anastomotic vessels have been shown to exist at all levels, superficially between the larger cerebral vessels of one side and across the midline to the other side, and at deeper levels in the vessels of smaller caliber, even the capillaries. So it may be that when local cerebral blood flow is interfered with, the patient may get along reasonably well as long as his anastomotic circulation is adequate. So we would like to know about the condition of the four large vessels carrying blood to the brain.

I would guess that no thrombosis will be found in vessels such as the middle cerebral artery; usually we are not particularly successful at demonstrating thrombosis in these vessels, despite infarction in the cortex or in the subcortex. Whether or not embolization was at work is another matter. Again, the Massachusetts General Hospital group has called our attention to the idea that emboli occur with considerably greater frequency in the central nervous system than we have heretofore suspected, and that we do not require a cardiac or pulmonary lesion to make this diagnosis, at least pathologically. It is possible for atherosclerotic disease to originate emboli, which then move up the circulation and produce infarction. Indeed, Adams and his co-workers[4,5] have indicated that embolization is frequently responsible for stroke, whereas previously we had attributed some 5 per cent of strokes to cerebral embolism. Whether or not this process was operating, I don't believe can be determined clinically; at least I wouldn't know how to determine it currently unless one did have a locus from which emboli might arise or there was other evidence for embolization, such as a pulmonary infarction.

I'll have to leave it with the idea that this man had multiple infarctions posterior to the rolandic fissure in the right parietal, occipital, and temporal lobes, and that there was not too much the matter with his frontal lobe. It would be my guess that no thrombosis will be found unless it is in one of the larger arteries and, in this case, I would think of the right internal carotid system. In addition, he had evidence of the Cushing phenomenon of erosion in the upper gastroenteric tract and paralytic ileus. Dehydration and metabolic acidosis were terminal events.

DR. TRUFANT: Dr. Aring, I suspect the students would agree with you that this was not a simple case. I say this on the basis of the diversity of opinion as to the diagnosis. All but six of the students agreed that cerebral atherosclerosis was at work. Nine students considered that softening of the brain, rather diffuse but particularly in the area of supply of the right middle cerebral artery, was operating. Five made a diagnosis of right internal carotid artery thrombosis, and three more that of an occluded right internal carotid artery discharging emboli in to the circulation. One student thought that there were multiple small thromboses in the right occipitotemporal area, another that there were multiple focal areas of softening about the rolandic fissure. I have one comment to offer in general about the written discussions, and that is the scant attention that was paid to the cortical nature of these seizures. Some men-

tioned it, but only a few discussed it; this is a crucial point in this case. The case is open for general discussion.

STUDENT: Dr. Aring, do you put any interpretation on this man's first bout of seizures beginning in 1938?

DR. ARING: I don't see how it can be brought together with what I would call the present illness. We have no hint whatsoever from the record that he had anything localizing at that time. We know that sudden diminution in the cerebral circulation may result in seizures, as for example in the Stokes-Adams syndrome, and it may be that such may happen with an infarction. If the 1938 episode was infarction, it was a silent one, and we don't have the evidence.

STUDENT: Could you explain how you believe the facial paresis occurred?

DR. ARING: (Drawing on board) I would think the lesion would have to be somewhere about the junction of the rolandic and sylvian fissures, near but not in the motor strip. Therefore, I postulated a lesion in the superior temporal gyrus. Had the lesion been in the motor strip, it seems to me he may have retained some evidence of it in later examinations. It also appears to me that a like process was at work to produce the hemianopia which came and went. I suspect that the optic radiations also were involved in the temporal lobe as they swing around the temporal horn of the ventricle on their way back to the occipital lobe. I can also envision that certain dynamic changes occurring with seizures may have disrupted subcortical functions but only temporarily.

STUDENT: My first thought was that the lesion was vascular in nature, but what do you have to say about multiple sclerosis as a possibility?

DR. ARING: It becomes increasingly improbable before the age of 15 and after the age of 55. In this case, it seems that the lesions are reasonably well clustered in an area of cortex; the disease is multiple in a sense but it isn't disseminated.

STUDENT: What is the nature of a disorder that can result in remissions of signs, for example hemianopia?

DR. ARING: Exhaustion paralysis, as with convulsion, diaschesis, and edema, is the usual explanation given. We really don't know what transpires to result in the remission in multiple sclerosis. With infarction it is thought that an embolus may disintegrate or anastomoses go quickly into operation to relieve the deficit.

STUDENT: What do you think of the possibility of a thrombus reducing the blood supply, then later becoming rechannelized, and the blood supply becoming re-established; does that happen?

DR. ARING: I'm sure it does, but it isn't much good unless anastomotic circulation comes into play quickly, because, as you know, neurons will die within a few minutes after being deprived of blood.

STUDENT: Is it very common to find a man with this many infarcts in his brain to have no mental change?

DR. ARING: I don't believe that the mental side was evaluated minutely in this man. The neurologic picture was obtrusive. With the lesions in his non-dominant hemisphere, he had no speech defect, so that he could exteriorize some of his thinking. When I saw him, as I think I did in February 1955, I was struck with his alertness. He was right with us and one could do a quite complete neurologic examination at that time. I am reasonably certain that we could have picked up defects with the Goldstein tests or the like, for example, defects in abstract reasoning; but we didn't go into this finer testing.

DR. J. PARK BIEHL: Is the dominant hemisphere of particular importance in intellectual functioning?

DR. ARING: I think it's mainly a matter of communication. I would not localize mental functioning in this manner.

PATHOLOGIC DISCUSSION

DR. JOSEPH SMITH: I'm afraid I find nearly all clinical pathologic conferences difficult when it comes to providing an answer

for all the clinical findings, and this one was no exception. At the time of necropsy, the first problem was to decide whether the surgeon or the internist had been right, since they had been in some disagreement as to the nature of the abdominal condition, the surgeon maintaining that there was an obstruction present and the internist being in some doubt about that. There did appear to be some obstruction in the lower ileum; there was a marked dilatation of the ileum and of the jejunum on opening the abdomen, and there was a definite twist with a band near the junction of ileum and cecum; the band was not fixed at both ends, but it appeared to have acted to some extent as an anatomic obstruction as the bowel was collapsed below this level. It appeared that the twist in the bowel at this site had not unravelled. On examining the alimentary tract a bit further, there was an extensive hemorrhagic necrosis in the mucosa of the stomach and patches in the small intestine. This type of acute hemorrhagic necrotizing gastroileocolitis (the involvement of the different segments varying in extent in different subjects), occurring in elderly debilitated people, sometimes with heart failure, has been described by Wilson and Qualheim.[6] In this patient I thought the hemorrhagic necrotizing gastritis and, to a certain extent, jejunitis and ileitis came first and was followed by ileus. As a result of the ileus, the twist in the bowel 6 cm. above the ileocecal valve could not unravel and a vicious circle of anatomic obstruction followed.

The heart weighed 520 gm. There was slight, chronic, rheumatic disease of the mitral valve, a definite thickening of the free margin of the valve, and shortening of the attached chordae tendineae but without stenosis. I did not note any antemortem thrombus in the auricular appendage or elsewhere in the heart. The left ventricle was 2 cm. thick and at the time I thought it was a hypertensive thickening, but on going through the history, there was very little evidence of hypertension. There was no disease of the aortic valve. There were scattered gray flecks of apparent fibrosis in the myocardium of the left ventricle, probably related to coronary atherosclerosis, although the atheroma in the coronary arteries was not particularly severe.

On microscopic examination these flecks of fibrosis were confirmed; many of them were perivascular in distribution. A very surprising thing for a man of 70 is that some were associated with groups of lymphocytes and histocytes and some of the latter had basophilic, twisted nuclei. They were in fact quite definite Aschoff nodules. As you know, these are specific for rheumatic carditis and are usually accepted as indicative of active disease.

I was not able to demonstrate any occlusion of the carotid arteries or of the vertebrals, but my examination was limited.

Now coming to the brain, I'll pass around the coronal slices that have been preserved, except those parts removed for histologic examination. On removal at necropsy a marked focal calcification of the falx cerebri was present and the leptomeninges were congested. The brain weighed 1485 gm. Since the coronal sections after fixation showed no ventricular dilatation, we can rule out general atrophy. Atheroma of the arteries at the base was not conspicuous, and there was no occlusion of any vessels. In the coronal slices a small focus of encephalomalacia was seen in the left caudate nucleus, but that does not explain a pill-rolling tremor of the left hand. The main change was in the more posterior part of the cerebrum, as Dr. Aring postulated. Here there was rather extensive old infarction involving the paracentral lobule and most but not all of the cortex posterior to this on the medial aspect of the cerebrum including the visual area. The lateral part of the posterior end of the temporal lobe and adjacent occipital lobe were also involved, but the inferolateral angle was spared. In these infarcted zones the cortex was greyish yellow and shriveled; it tended to become detached from the underlying white matter,

which was softer and a more opaque white than usual. The lateral geniculate body was not involved, but there was ample destruction in both optic radiation and visual cortex to explain the hemianopia. A further change was a 3 cm. slit in the white matter of the posterior end of the right middle temporal gyrus which had a smooth orange lining. No abnormality was found in the hind brain.

Do we get help from the microscopic examination to explain this infarction involving areas in anterior, middle, and posterior cerebral arterial distribution? Necrosis of the cortex was complete in places, in places laminar, and there were numerous proliferating astrocytes present. The latter were seen in the white matter where necrosis was partial and mixed with edematous areas. In the section of right middle temporal gyrus, the slit was bordered by a zone rich in hemosiderin-laden microglia cells as well as astrocytes. This focus could be a small old hemorrhage or an area of hemorrhagic infarction. Unfortunately, we did not get much help from the vessels. Most had widely patent lumina and in those in which it was decreased, the intimal proliferation was of a loose fibrous tissue with stellate cells but lacking iron pigment macrophages. This could have arisen from organization of old thrombotic or embolic lesions, but it is not typical. It is, however, rather more suggestive of this than of atheroma or arteriosclerosis. I have never been convinced that there is such a lesion as rheumatic cerebral arteritis,[7,8] so I am unwilling to use that as an explanation.

One further point. In the coronal slices there was slight dilatation of the anterior end of the right temporal horn with atrophy of adjacent hippocampus. Microscopically the cell loss was not conspicuous in this area and there were no prominent vascular lesions. I do not think this can explain the seizures dating back to 1938, although the slight atrophy here may have been a result of the convulsions.

My conclusions are, therefore, that the epilepsy dating from 1938 was idiopathic, and that the seizures and other neurologic disturbances in recent years were due to cerebral infarctions and possibly a small hemorrhage. The cause of the infarctions cannot be determined with certainty, but the facts that areas in the distribution of the anterior, middle, and posterior cerebral arteries were involved, that atheroma was not prominent, and that rheumatic heart disease was present suggest that multiple emboli occurred.

CLINICAL DIAGNOSIS

1. Multiple cerebral thromboses, right, on the basis of arteriosclerosis.
2. Bronchopneumonia.
3. Paralytic ileus.
4. Idiopathic epilepsy.

DR. ARING'S DIAGNOSIS

1. Multiple infarctions of right temporal, parietal, and occipital lobes on the basis of atherosclerosis.
2. Erosion of the upper gastroenteric tract (Cushing's ulcer).
3. Paralytic ileus.
4. Convulsive seizures of unknown etiology (onset in 1938).

PATHOLOGIC DIAGNOSIS

1. Encephalomalacia of right temporal, parietal, and occipital lobes. Cause undetermined but possibly due to multiple emboli.
2. Rheumatic myocarditis and mitral valvulitis.
3. Paralytic ileus. Necrotizing hemorrhagic gastroenteritis.

DR. RODMAN WILSON: I'd like to ask Dr. Smith to say something about how well the major arteries to the brain can be explored, and do we always explore them as well as we might?

DR. SMITH: In this hospital, we do autopsies before embalming and the morticians object strongly to dissection of carotid arteries in these circumstances, so you can do a sort of half-way job in that you can try to inject them from above and watch water come down from the lower ends.

You can palpate the carotid arteries in the neck; if there is a definite thrombotic occlusion of a main artery, I think we will pick it up. Perhaps as important as a complete occlusion is the severe atheromatous narrowing just above the bifurcation of the common carotid artery. That is where there seem to be major lesions; very often it is a severe atheromatous narrowing; I don't think we would pick that up unless we dissected the arteries. The vertebral arteries are never explored in the cervical spine except on a special occasion where a diagnosis of an aneurysm or the like has been made. The people who've done it have mostly chosen to take out the cervical spine, take it away, and spend perhaps a half day on it. You've got to do that sort of thing if you're going to make a study of vascular disease and probably you can only do it as a special study.

DR. ARING: Wouldn't the injection of ink or a colored solution in the proximal portions of both vertebral arteries as well as both internal carotid arteries, watching the aorta, give you a good deal of information?

DR. SMITH: It would tell you if there was a frank occlusion; it would not tell you whether there was severe narrowing.

DR. BIEHL: Do you think you could go further by injecting a radiopaque substance and x-raying?

DR. SMITH: You can, but to do that sort of study involves considerable time and labor. It is not practical in routine work; those who have made such investigations have done so as part of a research project.

DR. ARING: Were there any other infarctions in the viscera?

DR. SMITH: In this case, there were no other infarctions in the viscera; that is why I can't come out firmly for the diagnosis of multiple emboli as the cause of the cerebral infarctions, but I'm raising it as a possibility.

DR. ARING: I want to call attention, particularly of the students, to the superb articles on the cerebrovascular disorders emanating from the Massachusetts General Hospital.[2,4,5,9] I would expect that eventually their work will be put together as a monograph. I commend these articles to you; they have contributed to my better understanding of the process of stroke, although I must say that there remain a lot of questions still to be answered.

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CASE REPORT

Survival of a Patient with Central Nervous System Mucormycosis

William McCall, M.D. and Robert R. J. Strobos, M.D.

MUCORMYCOSIS of the central nervous system, or infection with the Phycomycete *Rhizopus oryzae*, is a rare occurrence. In human pathology the fungus has been known to invade the lungs, ears, or stomach. There have been 13 reported instances of mucormycosis of the central nervous system, all except one[1] ending fatally within a few days after onset.[2–9] The patient reported here is the second to have survived this complication for 12 months to date, in spite of considerable residual damage.

CASE REPORT

An 18 year old single white woman with diabetes, who had been taking 60 units of NPH insulin daily for one year, was admitted in a semi-comatose state with Kussmaul breathing. There was extensive ecchymosis and proptosis of the left eye (figure 1) of four days' duration. In addition, the left eye showed external and internal ophthalmoplegia and engorged retinal veins. The right eye was normal.

Urinalysis showed no protein, 4 plus sugar, and 3 plus acetone. The microscopic examination was negative. The blood sugar was 376 mg. per cent and the carbon dioxide was 4.6 mEq. per liter. Roentgen examination revealed pansinusitis.

A tentative diagnosis of cavernous sinus thrombosis was made. The patient was treated with antibiotics, anticoagulants, and insulin. The acidosis was reversed in ten hours and consciousness was regained. In view of the lack of response to antibiotic therapy and the typical clinical picture, however, the diagnosis of mucormycosis was suspected shortly and confirmed by culture of a purulent exudate from the left eye which grew *Rhizopus oryzae*.* On the fifth hospital day all antibiotics and anticoagulants were discontinued, and Mycostatin, 1 million units three times daily, was administered, followed by Parenzyme and potassium iodide. During the ensuing days complete right hemiparesis with marked aphasia developed gradually, together with stiffness of the neck. Several lumbar punctures indicated normal pressure, but showed a marked increase in the white blood cells (up to 10,000 per cu. mm. with 68 per cent polymorphonuclear cells in the acute phase) and in the total protein (maximal value of 117 mg. per cent). The cerebrospinal fluid sugar varied from 46 mg. per cent to 96 mg. per cent.

The left orbital tissue began to slough, with clear demarcation from the surrounding tissue. On the thirty-sixth day the left eye was eviscerated and the periorbital area was debrided under general anesthesia. At operation marked necrosis was found involving the left nasal bone, the infraorbital ridge, the frontal portion of the maxillary antral wall, the medial wall of the orbit, the left ethmoid and the sphenoid sinuses, and the nasal septum.

In vitro sensitivity studies showed the fungus to be completely resistant to penicillin, Erythro-

*Identified by Dr. Victor Cutter of the department of biology, Women's College of the University of North Carolina.

From the department of neurology, Bowman Gray School of Medicine, Winston-Salem, North Carolina.

FIG. 1. Photograph of the patient two days after admission, showing the swelling and beginning necrosis of the left periorbital tissue.

FIG. 2. Photomicrograph (x 360) of the hyphae of *Rhizopus oryzae* in the periorbital tissue.

mycin, and potassium iodide, but following the use of Mycostatin a zone of inhibition measuring 1.25 mm. was noted.

The patient was discharged 14 weeks after admission with improvement in the right-sided hemiparesis and residual aphasia. The orbital wound was clean and the diabetes well controlled. At present she is being followed closely in the out-patient department for control of the diabetes and further rehabilitation, and is being continued only on Mycostatin, insulin, and diet. Plastic reconstruction is planned at a future date.

Surgical specimen. Tissues from the left orbital contents and periorbital area and the nasal septum showed coagulation and liquefaction necrosis, with numerous granulocytes and macrophages. There was moderate fibrocytic proliferation and increased vascularity. Between the collagen bundles and in the vessel walls were small non-septate hyphae; acid-Schiff stain was positive (figure 2). Typically, the fungus hyphae grow in blood vessel walls in the gound substance between fibers, lifting up the internal elastic membrane and causing rupture and thrombosis.

COMMENT

In view of the increase in fungus diseases since the advent of antibiotics, it may be valuable to draw attention again to the easily recognized typical clinical picture of central nervous system mucormycosis. Usual course is as follows: A patient in diabetic acidosis manifests sinusitis, unilateral swelling and induration of the eyelids, proptosis, external and internal ophthalmoplegia, and subsequent necrosis. As the process spreads, signs of meningeal inflammation and focal cerebritis appear. Of the 13 reported cases, 11 showed the initial orbital inflammation described above, one presented focal involvment of the frontal lobe as an extension of ipsilateral sinus infection, and one presented a generalized systemic infection with multiple cerebral foci. In eight cases the presence of diabetic acidosis was proved and in another was probable, though data were incomplete. In three cases mucormycosis occurred as the terminal event after severe uremia, severe diarrhea and dehydration in an infant, and gallbladder surgery, respectively. In one patient the infection was systemic. There is no racial or sexual preponderance, and the ages range from two and one-half months to 75 years.

Central nervous system mucormycosis apparently does not occur except under debilitating circumstances and usually, but

not necessarily, in association with diabetic acidosis. It has been suggested that antibiotic therapy may enhance the growth of the fungus, a fact not substantiated in the present case by in vitro studies with Aureomycin, Erythromycin, streptomycin, penicillin, Achromycin, Terramycin, and bacitracin. There was moderate inhibition of growth with Polymyxin (60 micrograms) and slight inhibition with chloramphenicol (30 micrograms).

This patient's survival is of interest. The rapid compensation of the diabetic acidosis and the utilization of potassium iodide, parenzyme, and Mycostatin are believed to have been equally effective in controlling the infection.

SUMMARY

A patient with central nervous system mucormycosis complicating diabetes mellitus with acidosis is presented as the second known survival of this rare disease, although with considerable residual damage. The typical picture of central nervous system mucormycosis as drawn from the literature is given, and the factors predisposing to the condition are discussed briefly. Mycostatin is considered to be beneficial in infections due to *Rhizopus oryzae*.

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■ All that has been said of the posterior columns of the cord appears to apply equally to the restiform bodies – to the bodies which form the chief connection between these columns and the cerebellum, and not to those bodies only, but also to the small posterior pyramids of the medulla oblongata, which pyramids lie between the restiform bodies posteriorly. The connection between the cerebellum and the posterior columns of the spinal cord, which is made by means of the restiform bodies, is indeed such as to make it not improbable that the posterior columns perform for the cerebellum a similar office to that which is performed for the cerebrum by the anterior columns, or, in other words, that the posterior columns do for the involuntary movements of co-ordination what appears to be done for voluntary movements by the anterior columns.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

CASE REPORT

Subarachnoid Hemorrhage from an Aneurysm in a Patient with Thrombocytopenic Purpura

Edward C. Franklin, M.D., Marvin J. Powell, M.D. and Erich G. Krueger, M.D.

IN THE ABSENCE of hypertension, spontaneous subarachnoid hemorrhage is usually due to rupture of an intracranial aneurysm. Subarachnoid hemorrhage has only rarely been reported as a complication of thrombocytopenic purpura.[1]

The patient to be reported was admitted to the hospital with findings typical of a subarachnoid hemorrhage. In addition, a diagnosis of thrombocytopenic purpura was made. Because of the rare occurrence of subarachnoid hemorrhage in the course of thrombocytopenic purpura and the possibility of overlooking a surgically remediable lesion, carotid arteriograms were done which demonstrated an aneurysm of the right internal carotid artery at the origin of the posterior communicating artery. Conservative management of the aneurysm was elected initially, because of the danger of uncontrollable bleeding during the acute phase of the purpura. Hydrocortisone and splenectomy resulted in remission of the purpura. Because of the danger of recurrent subarachnoid bleeding, occlusion of the right internal carotid artery in the neck was performed one year later.

CASE REPORT

A 37 year old white male entertainer was admitted to the Bronx Veterans Administration Hospital on September 7, 1954. On August 27, 1954, during a theatrical performance, the patient noted the sudden onset of severe occipital headache and stiffness of the neck. Within a few minutes he perspired profusely, felt nauseated, and vomited. He sat down and several minutes later he lost consciousness and fell to the ground.

The patient was admitted to another hospital where he remained for ten days. He remembers little of what happened until his transfer to this hospital. Because of the history, signs of meningeal irritation, hyperactivity of the deep tendon reflexes on the right, and the findings of xanthochromic cerebrospinal fluid under increased pressure (table 1), a diagnosis of spontaneous subarachnoid hemorrhage had been made. The patient had been treated with complete bed rest and antibiotics until September 7, when he was well enough to be transferred to this hospital for further workup and treatment. From 1946 to 1950 the patient had received mecholyl iontophoresis and numerous vitamin preparations for morphea (circumscribed scleroderma). For the past two years he had noted easy bruisability.

Physical examination showed temperature 98° F., pulse 90 per minute, and blood pressure 130/85 mm. On admission the patient was found to be slightly disoriented, easily distracted, and with a poor memory for recent events. The skin showed several brownish areas of discoloration on the abdomen, back, and the extremities. These were identified as areas of morphea. There were no petechiae or hemorrhages into the skin. The heart and lungs were normal to percussion and auscultation. There was no hepatomegaly, splenomegaly, or lymph-

From the medical service and neurosurgical section of the surgical service, Bronx Veterans Administration Hospital, Bronx, New York.

TABLE 1
CEREBROSPINAL FLUID FINDINGS

Date	IP ($mm.H_2O$)	FP ($mm.H_2O$)	Color	Xantho-chromia	Protein (mg. %)	RBC (per cu. mm.)	WBC (per cu. mm.)	Polys	Lymphs
8/30/54	390	280	Salmon	1+	24	27,000	216	162	54
9/2/54	360+		Lighter	1+	77				
9/8/54	180	140	Xantho-chromic	2+	180	699	66	2	64
10/7/54			Clear	None	37	0	5		

adenopathy. A small flame-shaped retinal hemorrhage was present in the right eye. Neurologic examination showed mild central type facial paresis on the left, weakness of grip on the right, hyperactive deep tendon reflexes on the right, bilateral ankle clonus, and absence of pathologic reflexes. Sensory examination was within normal limits.

The patient was initially treated with bed rest. While under observation his mental status continued to improve. By the end of September the neurologic examination was entirely normal. Concomitantly, the cerebrospinal fluid returned to normal (table 1). The patient was then gradually allowed out of bed.

Because of the history of easy bruisability, the patient was transferred to the medical service on September 14, 1954. At that time the Rumpel-Leede test was strongly positive. The platelet count was 56,160 per cu. mm., bleeding time (Duke's method) one and one-half minutes, clotting time (Lee and White) four and one-half minutes, and clot retraction incomplete in 24 hours. Bone marrow examination on September 21 showed the cells of the myeloid and erythroid series to be normal in number and appearance. The megakaryocytes were normal in number and appearance, but there was absence of platelet clumps and shedding of platelets. Coombs' test was negative and L.E. cells were not found in the bone marrow or serum.

The course of the patient's purpura is graphically illustrated in figure 1. Without treatment there was a spontaneous rise of platelets and return of clot retraction to normal. However, the Rumpel-Leede test remained positive. Because of this, the patient was started on a course of hydrocortisone on October 19. There was prompt return of capillary fragility to normal within one day and no further rise in the platelet count.

On October 27, when the purpura was in complete remission, bilateral percutaneous carotid arteriography was done. The films demonstrated an aneurysm of the right internal carotid artery at its juncture with the posterior communicating artery (figure 2).

The patient was maintained on a daily dose of 60 mg. of hydrocortisone orally until November 3. The dose was gradually reduced and all medication discontinued on November 11. Within one day the Rumpel-Leede test again became positive. On November 30 he was found to have a platelet count of 21,600 per cu. mm. and incomplete clot retraction. Oral hydrocortisone was again started, with immediate reversion of the capillary fragility, platelet count, and clot retraction time to normal.

It was felt that long-term cortisone therapy, with its concomitant danger of producing hypertension, might increase the likelihood of future rupture of the aneurysm. Therefore, splenectomy was performed on December 17 to control the purpura. Hydrocortisone was discontinued on December 22 and there has been no recurrence of thrombocytopenia to date. Bone marrow examination on January 6, 1955 showed abundant megakaryocytes.

The spleen weighed 170 gm. and appeared grossly normal. Sections of the spleen showed conspicuous small lymphoid follicles. Occasional megacaryocytes were present in the pulp.

Surgical treatment of the aneurysm was not undertaken in the acute stage of purpura because of the risk of encountering uncontrollable bleeding. During the year following his discharge, the patient remained in good general condition. Because of the danger of recurrent hemorrhage the patient was readmitted to the neurosurgical section on December 6, 1955. Laboratory studies and medical re-evaluation at that time showed no evidence of thrombocy-

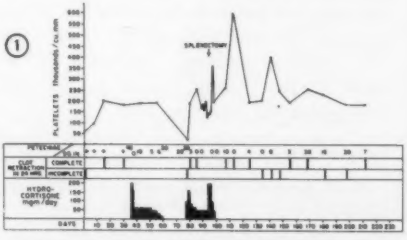

FIG. 1. Course of patient with thrombocytopenic purpura.

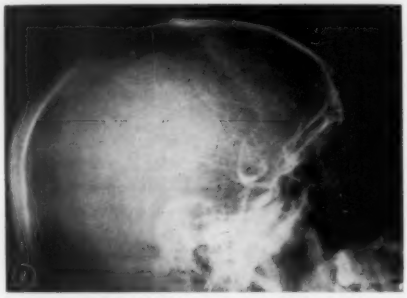

FIG. 2. Right lateral arteriogram demonstrating aneurysm at origin of posterior communicating artery.

topenic purpura and the neurologic examination revealed no abnormalities.

A right cartoid arteriogram again demonstrated the aneurysm, which had diminished somewhat in size. On December 14, 1955 a Selverstone clamp was applied to the right internal carotid artery in the neck and gradual occlusion of the artery was accomplished within four days without complication. On January 15, 1956 a left carotid arteriogram was done. It showed good filling of the ipsilateral cerebral vessels and the right anterior cerebral artery, but only partial filling of the right middle cerebral artery, without retrograde filling of the right internal carotid artery and its aneurysm. A subsequent vertebral arteriogram established the fact that the blood supply of the right middle cerebral artery was derived largely from the right posterior communicating artery. Intracranial attack on the aneurysm, either by trapping or ligation at the aneurysmal neck, was not undertaken, because of the possibility of impairing the blood flow through the posterior communicating artery and thereby producing hemiplegia. On his discharge in January 1956, as well as on subsequent follow-up examination as late as June 1956, the patient remained symptom free.

COMMENT AND CONCLUSIONS

It is felt that the subarachnoid hemorrhage in the reported case originated from a rupture of the arteriographically demonstrated aneurysm of the right internal carotid artery and was not caused by the coexisting blood dyscrasia. By the end of one year approximately 50 per cent of all patients with spontaneous subarachnoid hemorrhage will have died, either in the primary or a recurrent attack.[2] It appears that this high mortality can be reduced only by direct occlusion of the aneurysm or ligation of the afferent artery in carefully selected cases.[3] The intracranial approach to lesions in this location is hazardous. Because of the added danger of encountering uncontrollable bleeding due to thrombocytopenia, conservative management was chosen in the acute phase of the disease. In spite of the fact that the patient was asymptomatic during the year after his discharge, the possibility of recurrent subarachnoid bleeding from the aneurysm persisted. Therefore, occlusion of the right internal carotid artery in the neck was carried out without complication. A planned intracranial attack was abandoned after postoperative evaluation of the circulation of the circle of Willis by carotid and vertebral arteriography.

This case again illlustrates the fact that spontaneous subarachnoid hemorrhage is usually due to rupture of an intracranial aneurysm. Such a lesion should be suspected in every case, even though an apparently adequate cause for the bleeding has been demonstrated. If thrombocytopenia had been accepted as the etiologic factor, no further search for an aneurysm would have been undertaken and a serious condition with potentialities for surgical correction would have been overlooked.

SUMMARY

1. A case of spontaneous subarachnoid hemorrhage due to rupture of an intracranial aneurysm in a patient with thrombocytopenic purpura is reported.

2. It is the authors' opinion that it is imperative to search for an aneurysm in all cases of subarachnoid hemorrhage, even though an apparent cause for the bleeding has been found.

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CASE REPORT

Congenital Dermal Sinus Complicated by B. Proteus and Nonhemolytic Streptococcus Meningitis

E. Peyser, M.D., W. Cohen, M.D. and A. Y. Joseph, M.D.

CONGENITAL DERMAL SINUSES represent remnants of incomplete closure of the neural crest during embryonic life. They usually manifest themselves as narrow tracts extending from the skin surface down toward the central nervous system. While most common in the lumbosacral region, they may appear at a higher level of the neural axis, particularly in the cervical and occipital regions. These tracts begin in the midline with a small dimple in the skin leading down to various depths and they may or may not be connected with the central nervous system. They are lined with epidermis and may contain in their walls all the adnexae of normal skin including hair (pilonidal cysts, dermoids). They remain symptomless unless they compress nervous tissue or become infected.

This report deals with an unusual meningeal infection originating from a spinal dermal sinus, and the presentation will be limited to this location of the disorder.

Moise[1] in 1926 was the first to report an infected congenital dermal sinus complicated by staphylococcal meningitis. Diagnosis was confirmed by operation and the 18 year old patient made a complete recovery, although this was before the era of chemotherapy. Since Moise described his case, 44 additional cases of spinal dermal sinus have been reported in the literature.[2–6]

In 19 of the 45 reported cases the sinus terminated as an epidermoid or dermoid cyst without entering the spinal canal. In the remaining 26 cases there was more intimate relationship between the sinus and the contents of the spinal canal. It either communicated directly with the spinal cord or ended in the epidural or subdural space. In 29 cases the sinus was infected. In those patients in whom the sinus tract was closely related to the spinal cord or its coverings, the infection caused either generalized meningitis or epidural or subdural abscess.

The various organisms described as causing the infection were *Staphylococcus albus, Staphylococcus aureus, Pneumococcus, E. coli, Hemophilus influenzae,* and *Diphtheroids.* In several cases there was a mixed infection with two[7] or even three organisms, as in Perloff's[5] case in which meningitis was caused by hemolytic *Staphylococci* (coagulase positive), nonhemolytic *Staphylococci,* and *Pneumococci.* As far as we could ascertain from the literature, no case has yet

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been reported in which either *B. proteus* or nonhemolytic *Streptococci* were the infecting organisms.

A case of mixed meningitis is presented which illustrates the importance of suspecting a dermal sinus as the source feeding an infection whenever a purulent meningitis does not respond to appropriate antibiotic therapy or is caused by more than one organism.

REPORT OF CASE

A four and one-half year old boy was admitted to the Hadassah Hospital in Beersheba on January 19th, 1956. About a week prior to admission he had fallen from his brother's shoulders and two days later he began to complain of pain in his back. On the day preceding admission he started to suffer from headaches, he vomited several times, and his temperature rose to 39° C. On examination his general condition was fairly good. There was marked nuchal rigidity and general hyperesthesia. In the lower lumbar region a small dimple was detected in the midline. On further interrogation the patient's mother admitted that this region had occasionaly been tender, but no discharge had ever been noticed.

Roentgenograms of the spine revealed a slight degree of spina bifida occulta at the fifth lumbar vertebra. There were 27,500 white blood cells in the peripheral blood, with a moderate shift to the left in the differential count. Lumbar puncture yielded cloudy spinal fluid containing 8,000 white cells, mostly neutrophils. A smear showed gram-negative bacilli and gram-positive cocci which were identified by culture as *B. proteus* and nonhemolytic *Streptococci*.

A diagnois of mixed meningitis was made and antibiotic therapy was started with streptomycin and chloramphenicol, based on in vitro sensitivity of the microorganisms. Since there was no clinical improvement in the patient's condition over the next few days, bacitracin and polymyxin were added both systemically and intrathecally. However, there was no essential change in the child's condition. On January 29 he was transferred to the Rothschild Hadassah University Hospital in Jerusalem. Antibiotic therapy was continued and Neomycin[8] was given in addition both intramuscularly and intrathecally. His temperature remained high and there was no improvement in the signs of meningeal irritation. There were no focal neurologic signs referable to the brain or spinal cord. Roentgenograms of the skull were normal, and an electroencephalogram was negative except for diffuse slow activity with no focal accentuation. A sinus was suspected under the dimple in the patient's back, but an attempt to fill it with Lipiodol was unsuccessful. Repeated cerebrospinal fluid cell counts varied between several hundred to several thousand white blood cells. Both *B. proteus* and nonhemolytic *Streptococci* continued to be cultured.

On February 21 a small subcutaneous abscess was seen in the region of the dimple. About 1 cc. of thick yellow pus was aspirated, from which eventually the same microorganisms were cultured. Surgical intervention was decided upon, since it had become obvious that the infection would not subside with conservative therapy.

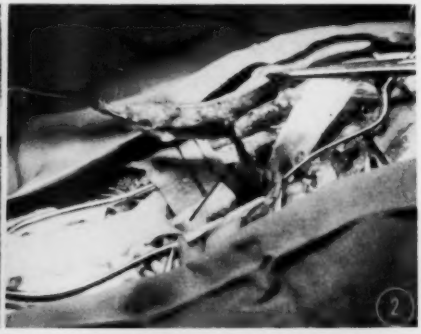

FIG. 1. Excision of skin area around dimple in lower lumbar region, showing narrow tract attached to it.
FIG. 2. Dissection of tract down to the spinous process of the fifth lumbar vertebra. A cystic dilatation was visualized at its lower end.

Operation. On February 22 the skin area around the dimple was excised (figure 1) and a narrow tract attached to it was visualized. Dissection of the tract was pursued down to the spinous process of the fifth lumbar vertebra, which was partly bifid. Laminectomy of the fifth, fourth, and third lumbar vertebrae was performed. The whole tract was thus dissected and a cystic dilatation was visualized at its lower end (figure 2). Just as it entered the dura it became narrow again. The dermal sinus was completely excised and the dura opened. A fairly large subdural abscess was entered and its contents evacuated. The same organisms producing the meningitis were cultured from this pus. As the abscess cavity was being irrigated, the nerve roots of the cauda equina could be seen stuck together in a fibrinopurulent exudate. No attempt was made to separate the adhesions. The dura was closed tightly, a drain was left in the epidural space, and the wound was then closed in layers.

Postoperatively temperature came down to normal within two days. There was hardly any discharge along the drain, which was shortened on the second postoperative day and removed on the fifth. All the meningeal signs disappeared rapidly and the patient made an uneventful recovery with no neurologic deficit. Lumbar pucture on the twelth day after the operation yielded clear sterile fluid. Histologic examination of the surgical specimen revealed evidence of acute and chronic inflammation of the tract which was lined with epithelium. The cystic dilatation was filled with cell detritus and hair. The patient was discharged from the hospital two weeks after surgery and has been followed in the outpatient clinic for three months. There has been no recurrence of symptoms and he has remained in good health.

SUMMARY

A case of meningitis in a four year old boy is described, caused by *B. proteus* and nonhemolytic *Streptococci*. An infected congenital lumbar dermal sinus was found to be the source of the meningeal infection. Conservative therapy with a wide variety of antibiotics was unsuccessful. Radical excision of the anomaly resulted in complete recovery. It is stressed that a dermal sinus should be suspected when meningitis is due to mixed infection or does not respond to appropriate antibiotic therapy.

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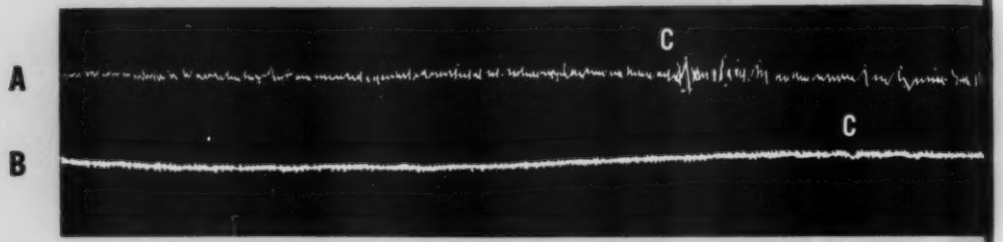

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1. Dickel, H.A., et al.: West. J. Surg., April, 1956.

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APRIL 1957

Boston Group Poised For AAN Influx

With Joseph Foley heading local arrangements, the Boston group of neurologists are poised to receive the largest and the most widely ramified neurologic gathering ever held in the United States - the ninth annual meeting of the American Academy of Neurology at the Sheraton-Plaza Hotel in Boston (April 22-27). A rapidly expanding AAN membership, a new vigor and collaboration in neurology and the neurologic sciences, combine to set the pace of this unprecedented reunion.... Eight-two papers comprise the central core of the scientific sessions - papers carefully selected by James L. O'Leary and his program committee from more than twice that number from all parts of North America, from Europe, and from such distant lands as Iran, Syria, Israel, Turkey, and Argentina.... While it is difficult to highlight titles in a program so compact and so competitive, yet it is equally difficult not to point to such topics as the collateral regeneration of motor nerve fibers by Wohlfart (Sweden); radioisotopic studies in nucleoprotein metabolism by Koenig; localization of radioactive isoniazid by Barlow, Schooler, and Roth; collimation detection of brain tumors by Shy, Bradley, and Matthews; the distribution of radioarsenic in normal and tumor tissues by Brownell, Sweet, and Mealey; the integration of movement by Denny-Brown; the psychic aspects of higher brain functions by Halstead; and cortical sensorimotor organization by Woolsey. These presentations are only part of the package; the rest can be scanned by glancing through the outline of the program contained in the March issue of NEUROLOGY. Note the interesting collection of papers on the neurologic disorders of childhood.

Neurochemistry Section To Inaugurate Program

Besides the eighty-two papers constituting the central core of the scientific sessions, the Boston AAN meeting will witness the inaugural program (an additional thirty papers) of the Academy's newly created section on neurochemistry, which will be conducted simultaneously with the general sessions. The program will present timely topics of interest in this newly developed discipline. Among them are: the relationship of ceruloplasmin to Wilson's disease by Scheinberg, Harris, and Dubin; muscle proteins in dystrophy by Horvath; a series of studies on lipid metabolism, including studies on the biosynthesis of galacto-

lipids, by Burton, Sodd, and Brady; and myelination and demyelination from the standpoint of lipogenesis by nervous tissues in vitro by Manjo and Karnovsky. Also of timely interest are such topics as the mode of action of an inhibitor of acetylcholine synthesis by MacIntosh, Birks, and Sastry, and the central interaction of tranquilizing and hallucinogenic drugs with serotonin and norepinephrine by Bogdanski, Spector, Shore, and Brodie. These are only samples of many interesting topics to be presented by the neurochemists.... On Friday, April 26, a colloquium on the development of neurochemistry will be held under the chairmanship of Donald B. Tower. The program will feature papers by Forster, Tower, McIlwain, Rossiter, and Wilson.... J. Folch-Pi and Alfred Pope offer an informal open house in their laboratory at McLean Hospital, Saturday afternoon, April 27.... The neurochemistry section of the AAN was organized by Donald B. Tower after the St. Louis meeting (April 23-28, 1956).

61 Exhibits and Demonstrations To Round Out Scientific Sessions

The unique skill and drive of Louis D. Boshes, chairman of exhibits, will bring to the Boston AAN meeting 61 high quality exhibits and demonstrations (36 scientific exhibits and demonstrations, three exhibits by voluntary health agencies, and 22 technical exhibits by pharmaceutical and electronic instrument companies and medical publishers).... The range of topics covered by the scientific exhibits and demonstrations comprise by themselves a full neurologic education; from growth of the brain, the scientific displays pass by way of pictographs of modern concepts developed from many disciplines in experimental neurology, to the applied field of newer methods of disease, diagnosis, and management.... Four serial section displays (by Yakovlev and his co-workers) on human stereotactic coordinates, surgical pathology, encephalopathies, and brain anatomy will be shown in the Warren Anatomical Museum at Harvard.... A special room has been set aside for motion pictures and demonstrations. Among the former are chemopallidectomy (Cooper); electronic pupillography (Lowenstein); hemiballismus (Strain and Perlmutter); thyrotoxic myopathy (Rosenbaum and Levy); and the effects of methocarbamol on muscle (Vazuka). Among the latter are aids for Parkinson's disease (Schwab and associates); modified pneumoencephalography (Thomas); new approach to trigeminal neuralgia (Willard); hemato-encephalic exchange as a function of age (W. A. Himwich), and EEG studies on asphyxiated guinea pigs (Marisa I. R. Ramirez de Arellano).... The voluntary health societies exhibiting are the Muscular Dystrophy Associations of America, the Rhode Island Society for Crippled Children and Adults, and the National Society for Crippled Children and Adults.

Joseph N. Welch to Address Combined Luncheon

Joseph N. Welch, distinguished Boston attorney, will address the combined luncheon of Academy members and the Woman's Auxiliary, Thursday, April 25. Born on an Iowa farm, Mr. Welch graduated from Grinnell College and later from the Harvard Law School. He has practiced law in Massachusetts since 1919 when he joined the firm of Hale and Dorr, specializing in the trial of cases before state and federal courts as an authority on the law of libel.... Mr. Welch attained national renown among television viewers because of his legal agility and the courtly grace and charm he presented as chief defender of the Army during the McCarthy hearings. He is a well known television narrator and has appeared on Ed Murrow's program, "See It Now."

Conference on Neurologic Training To Follow AAN Meeting

Immediately following the AAN meeting at the Sheraton-Plaza in Boston, 90 directors of neurologic training programs, basic neurologic scientists, and medical educators will convene at the same hotel (April 27-29). The general purpose of the conference, which is to be chaired by Adolph L. Sahs, is to review progress in neurologic training during the past year and blueprint future objectives. This conference is the second of its kind, the first having been held prior to the AAN meeting in St. Louis (April 23, 1956 - Newsletter, March 1956). The second conference is being sponsored, as was the first, by the National Institute of Neurological Diseases and Blindness.... After the general review session on Saturday afternoon (April 27), the conferees will split into a series of panels for the consideration of specific problems. On Monday morning (April 29), reports and conclusions of the panels will be given, which will be followed by a general discussion by the conferees.... A planning meeting for the conference was held in Chicago (March 25).

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Grants for Travel to International Congress

Grants-in-aid to partially defray travel expenses of top scientists wishing to attend the First International Congress of Neurological Sciences in Brussels (July 21-28, 1957 - Newsletter, November 1956) have been made by the National Science Foundation in cooperation with the National Committee for Research in Neurological Disorders. Also, the Office of Naval Research has made available transportation facilities to a limited number of candidiates.... More recently, as a result of an application from the American Academy of Neurology, the National Advisory Neurological Diseases and Blindness Council has earmarked funds for a grant to help defray the cost of travel for a selected number of neurologic teachers and investigators who wish to attend the Brussels Congress. This grant is

designed to assist clinical neurologists and scientists whose major interest is in academic neurology. Applicants for these grants should forward a letter at the earliest possible date, stating their major field of interest, the purpose to be achieved by attending the conference, together with a curriculum vitae, to the Director, National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland.... Registration at the Congress is $15 (active); $10 (associate); $5 (auxiliary). The registration fee includes attendance at the scientific sessions and all official receptions and social functions, except the fee for the banquet and dance (July 25), which is $9 per person. Attendance at the dance only is $2 per person. Payment of fees for the banquet and dance must be made at the same time as payment of the registration fee.

Conference on Aging Process in the Nervous System Thirty distinguished investigators met in Bethesda (January 30-February 1, 1957) to summarize the present state of knowledge and chart the future course of research on the aging process in the nervous system. Held under the sponsorship of the NINDB Advisory Council, the conferees reviewed recent developments in this field, emphasizing the need for better nerve cell staining methods, more detailed knowledge of the relationships between nerve cells and the synapse, and for the establishment of a method for acquiring experimental animals of known age. Participating in the conference were: Honorary Chairman E. V. Cowdry; H. A. Imus, W. F. Windle, and J. E. Birren, co-chairmen; Robert W. Albers, John E. Anderson, Warren Andrew, L. B. Arey, Harry W. Braun, Harold Brody, Robert H. Brownson, Jan Cammermeyer, Edward W. Dempsey, Donald Duncan, J. E. Fazekas, Louis B. Flexner, Harold E. Himwich, Albert I. Lansing, H. W. Magoun, Ross A. McFarland, Elizabeth K. Moyer, Alfred Pope, Nathan W. Shock, Louis Sokoloff, Lewis D. Stevenson, Eugene Streicher, Norman M. Sulkin, Raymond C. Truex, Harry H. Wilcox, and Abner Wolf.

Conference on Encephalitis A conference on the sequelae of arthropod-borne encephalitides, organized and sponsored by the National Institute of Neurological Diseases and Blindness, will take place in Bethesda (April 19, 1957). The purpose of the conference, under the chairmanship of Joseph E. Smadel, associate director of the National Institutes of Health, is to develop methodologies for the recording of data and follow-up studies, both retrospective and anterospective, in this field. Among the participants are Albert Sabin, C. M. Eklund, A. B. Baker, Knox Finley, J. Earl Smith, and Sidney Farber.

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